PHARMACOECONOMIC EVALUATION OF ORAL ANTIDIABETICS FOR AMBULATORY PATIENTS IN A TERTIARY HOSPITAL

A Dissertation work submitted to

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In partial fulfillment of the requirements for the award of degree of

MASTER OF PHARMACY IN

(PHARMACY PRACTICE)

Submitted by

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ABBREVIATIONS

DM	-	Diabetes Mellitus
T2DM	-	Type 2 Diabetes Mellitus
CEA	-	Cost Effective analysis
CBA	-	Cost Benefit Analysis
CUA	-	Cost utility Analysis
FBS	-	Fasting Blood Sugar
RBS	-	Random Blood Sugar
PPBG	-	Post parandial Blood Glucose
HbA1c	-	Glycated Heamoglobin
QALY	-	Quality Adjusted Life Years
ACER	-	Average Cost Effective Ratio
ICER	-	Incremental Cost Effective Ratio
DPP4	-	Dipeptidyl Peptidase 4 Inhibitor
NICE guidelines	-	National Institute for Health and Care Excellence.
mmol/l	-	Milli moles/ litre
CVD	-	Cardiovascular Disease
HTN	-	Hypertension
CAD	-	Coronary Artery Disease
ACS	-	Acute Coronary Syndrome
UTI	-	Urinary Tract Infection
COPD	-	Chronic obstructive Pulmonary Disease
TZD	-	Thiazolidinediones

ID	-	International Dollars
USD	-	United States Dollars
INR	-	Indian Rupee
AZT	-	Azidothymidine

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

PHARMACOECONOMICS

Pharmacoeconomics is the scientific discipline that evaluates the clinical, economic and humanistic aspects of pharmaceutical products, services and programs as well as other health care intervention to provide health care decision makers, providers and patients with valuable information for optimal outcomes and allocation of health outcomes.

History:

The term Pharmacoeconomics was first time used in public forum was in 1986, at a meeting of pharmacists in Toronto, Canada, when Ray Townsend from the Upjohn company, used the term in presentation. Ray and few other had been performing studies using the term pharmacoeconomics within the pharmaceutical industry since the early eighties today pharmacoeconomics research is a flourishing industry with many practitioners, a large research and application agenda, several journals and flourishing professional societies including the international society for pharmacoeconomics and outcomes research. Why did the term catch on? The pharmacoeconomics started with a study of the cost-effectiveness of AZT for the treatment of persons with AIDS.

ECONOMIC BURDEN OF DIABETIS MELLITUS

Diabetes Mellitus is one of the leading epidemics globally. Most people are affected by this disease. It is associated with high mortality and morbidity rates as well as high economic use. The total annual cost for Australians with type 2 diabetes is up to $6 billion including healthcare costs, the cost of careers and Commonwealth government subsidies. The average annual healthcare cost per person with diabetes is $4,025 if there are no associated complications. [1]

In India according to the study done by Jitendrah Singh the following observation was made that the average expenditure per patient per year would be a minimum of INR 4,500 (approximately US $120). Therefore, the estimated annual cost of diabetes care would be approximately 180,000 million INR. [2]The prevalence of diabetes in 2013 in India was only slightly higher than the world average (9.1% vs. 8.3% worldwide). [3] However, due to its very

large population, India has the world's largest population living with diabetes after China. In 2013, there were 65.1 million people between 20 and 79 years of age with diabetes and this number was predicted to rise to 109 million by 2035. The growing epidemic of type 2 diabetes in India has been highlighted in several studies. [4]

Diabetic Mellitus in rural and urban areas

A study in Indian patients by Ramachandran et al analyzed the urban-rural expenditure on diabetes. The study indicated that the economic burden of diabetes care on families in developing countries is rising rapidly, even after accounting for the inflation. The annual family income was higher in urban subjects [rupees (Rs) 100,000 or $2,273] than in the rural subjects (Rs 36,000 or $818) ($P < 0.001$). Total median expenditure on health care was Rs 10,000 ($227) in urban and Rs 6,260 ($142) in rural (P0.001) subjects. [5] Another study showed that the lower treatment expenditure in rural may be due to issues of less access and affordability rather than lower need as assumed and late detection of the disease in these settings often leads to catastrophic spending for individuals and households [6]. Socioeconomic differences and the urban–rural divide suggest divergence in disease outcomes. In other words, the relatively wealthier population living in urban areas spend more on diabetes care and have better outcomes, while relatively poorer people living in rural areas tend to have more difficulties accessing diabetes care, and therefore spend less on diabetes care and tend to have worse health outcomes [7]

Out of pocket expenditure

Out of pocket expenditure refers to patients accessing treatment facilities by spending from their own pockets which is a very common practice in India. In developed countries most of their health bills are covered b the health insurance companies. Here in India efforts to provide health insurance are ongoing and studies have shown that including the private health care up to 25% that is 300 million people are covered up to 2012. [8] Therefore the financial burden still falls on the individuals since the health insurance is not covering fully. Studies estimate that, for a low income Indian family with an adult with diabetes, as much as 20 percent of family income may be devoted to diabetes care. For families with a diabetic child, up to 35 percent of income is spent on diabetes care. If you have Diabetes for five years you would have spent around Rs

1,50,000 on diabetes treatment only. After 10 years you would have spent Rs 4,00,000 and after 20 years you would have spent Rs 15,00,000. The increase in cost with time is due to the increase in complications.

Therefore Diabetes Mellitus is an expensive disease to treat and it is one of the growing pandemic in the world because of the changing lifestyles. Therefore means to cope with the disease should be enhanced. Need for getting cost effective means of treating diabetes Mellitus is uncompromisable because even though the patients improve on their symptoms, the cost is burdening them.

Diabetes Mellitus

Definition

Diabetes Mellitus is a chronic metabolic disease characterized by hyperglycemia which is high blood sugar which may be as a result of insulin resistance or reduced insulin production or both. Insulin hormone is used to lower the blood sugar preventing the hyperglycemia

Types

1. **Type 1 Diabetes Mellitus**

   This is also known as insulin dependent diabetes which is as a result of low insulin production from the beta cells of the pancreas which is accredited to autoimmune destruction. Therefore the blood sugar is not utilized or converted to glycogen thus it becomes much in the blood. This type is only treated with Insulin.

2. **Type 2 Diabetes Mellitus**

   Also known as insulin independent diabetes mellitus. In this the insulin production is present however there is resistance towards the insulin therefore it is not utilized and thus the blood sugar becomes relatively high in blood because glucose is not utilized by the cells.

SYMPTOMS

- **Increased thirst and frequent urination.** Excess sugar building up in your bloodstream causes fluid to be pulled from the tissues. This may leave you thirsty. As a result, you may drink — and urinate — more than usual.
- **Increased hunger.** Without enough insulin to move sugar into your cells, your muscles and organs become depleted of energy. This triggers intense hunger.
- **Weight loss.** Despite eating more than usual to relieve hunger, you may lose weight. Without the ability to metabolize glucose, the body uses alternative fuels stored in muscle and fat. Calories are lost as excess glucose is released in the urine.
- **Fatigue.** If your cells are deprived of sugar, you may become tired and irritable.
- **Blurred vision.** If your blood sugar is too high, fluid may be pulled from the lenses of your eyes. This may affect your ability to focus.
- **Slow-healing sores or frequent infections.** Type 2 diabetes affects your ability to heal and resist infections.
- **Areas of darkened skin.** Some people with type 2 diabetes have patches of dark, velvety skin in the folds and creases of their bodies — usually in the armpits and neck. This condition, called acanthosis nigricans, may be a sign of insulin resistance

RISK FACTORS

- **Weight.** Being overweight is a primary risk factor for type 2 diabetes. The more fatty tissue you have, the more resistant your cells become to insulin. However, you don't have to be overweight to develop type 2 diabetes.
- **Fat distribution.** If your body stores fat primarily in your abdomen, your risk of type 2 diabetes is greater than if your body stores fat elsewhere, such as your hips and thighs

- **Inactivity.** The less active you are, the greater your risk of type 2 diabetes. Physical activity helps you control your weight, uses up glucose as energy and makes your cells more sensitive to insulin.
- **Family history.** The risk of type 2 diabetes increases if your parent or sibling has type 2 diabetes.
- **Race.** Although it's unclear why, people of certain races — including blacks, Hispanics, American Indians and Asian-Americans — are more likely to develop type 2 diabetes than whites are.
- **Age.** The risk of type 2 diabetes increases as you get older, especially after age 45. That's probably because people tend to exercise less, lose muscle mass and gain weight as they age. But type 2 diabetes is also increasing dramatically among children, adolescents and younger adults.

Drugs used to treat diabetes mellitus

Table 1: Classification of oral antidiabetic drugs

Class	Mechanism	Agents	Advantages	Disadvantages
Biguinides	Decrease hepatic gluconeogenesis	Metformin	No hypoglycemia, weight neutral	GI disturbance, lactic acidosis
Sulphonylureas	Stimulate insulin secretion	Glimepiride, gliclazide, glibenclamide, etc	Inexpensive	Hypoglycemia, weight gain
Meglitinides	Stimulate insulin secretion	Repaglinide nateglinide	Short onset of action, low postprandial glucose	Hypoglycemia
α-Glucosidase inhibitors	Decrease glucose absorption	Acarbose, voglibose	Reduce postprandial glucose	GI flatulence
Thiazolidinediones	Improve insulin resistance	Pioglitazone	Lower insulin requirements	Edema, CHF, weight gain, fracture, macula edema
DPP 4 inhibitors	Prolong GLP-1 action	Sitagliptine, vildagliptine, saxagliptine, linagliptine	No hypoglycemia	Less clinical experience

COSTS OF TREATING DIABETES MELLITUS

Treating Diabetes Mellitus entails both the medical and non medical costs put in consideration. Medical costs are those that directly affect the medical aspect of the disease where as the non medical costs are those that indirectly affect the treatment of diabetes mellitus they are contributing factors.

Medical Cost

a. Cost of antidiabetic drug
b. Cost of laboratory tests
c. Cost of physicians and nurses
d. Cost of complications
e. Cost of hospitalization

Non Medical costs

a. Cost of transportation
b. Work loss days (absenteeism) and low productivity during working days due to disease.
c. Cost experienced by care givers during hospitalization.

A. Cost of oral antidiabetic drugs

1. BIGUANIDES

These are the mostly used first line antidiabetic agents. They are preferred because of their benefits. Patients on this drug have lower rates of cardiovascular disease and mortality compared to patients on sulphonylureas. Metformin delays progression to diabetes in persons with impaired glucose tolerance. It has also been used in treatment of infertility in women with polycystic ovarian syndrome. It improves ovulation and menstruation cyclicity and reduces circulating androgens and hirsuitis.

Studies have also shown that metformin is one of the cost effective therapies in treating type 2 diabetes mellitus. Both lifestyle modification and metformin were cost-effective interventions for preventing diabetes among high risk-individuals in India and perhaps may be useful in other developing countries as well. [2]

Other studies showed that when metformin was used in combination with other drugs it was cost effective than metformin used singly. A study done in Kenya by Gerald Ochieng showed that using combination therapy of Metformin and a DPP4 Inhibitor was more cost effective than monotherapy of metformin. [10]Similarly treating DM with combination of metformin + glimepride was the most cost effective in another study. [11]

2. SULPHONYL UREAS

Drugs in this category include glimepride, glicizide and Glibenclamide. These Drugs are second line therapy and are used as add ons drugs to Metformin .Adding sulphonylurea to metformin targeted both insulin resistance and insulin deficiency. Sulphonylurea was efficacious and cheaper than thiazolidinedione, dipeptidyl peptidase-4 inhibitor, glucagon-like peptide 1 analogue and insulin. The main side effect of sulphonylurea was hypoglycaemia but there was no effect on the body weight when combining with metformin. Fixed dose sulphonylurea/metformin was more efficacious at lower dose and reported to have fewer side effects with better adherence. Furthermore, fixed dose combination was cheaper than add-on therapy. [[12]

3. MEGLITINIDES

Melglitinides are also known as insulin secretagogues. They include repaglinide and Nateglinide. These drugs have been seen to be more cost effective than sulfonyl ureas because of the sulfonyl ureas side effects e.g. Weight gain and hypoglycemia. The NICE guidelines on Type 2 Diabetes Mellitus – critical analysis supports the use of Meglitinides as a first line therapy in patients who are contraindicated to metformin and as a second line agent to metformin instead of sulfonyl ureas as was normal clinical practice. [29]

4. ALPHA GLUCOSIDASE INHIBITORS

Of all available anti-diabetic drugs, α-glucosidase inhibitors seem to be the most effective in reducing post-prandial hyperglycemia. They include Acarbose, Voglibose. A study carried out by Gussepe et al on alpha Glucosidase inhibitors showed that although the drug acarbose is expensive in comparison to other antidiabetic drugs it has good benefits. α-Glucosidase inhibitors can be used as a first-line drug in newly diagnosed type 2 diabetes insufficiently treated with diet and exercise alone, as well as in combination with all oral anti-diabetics and insulin if monotherapy with these drugs fails to achieve the targets for HbA_{1c} and post-prandial

blood glucose. As a first-line drug, they are particularly useful in newly diagnosed type 2 diabetes with excessive PPG, because of their unique mode of action in controlling the release of glucose from complex carbohydrates and disaccharides. α-Glucosidase inhibitors may also be used in combination with a sulfonylurea, insulin or metformin.[13]

5. Use of Newer drugs in Diabetes Melitus - DPP4 inhibitors

These are the newer drugs in the field of diabetes mellitus with less clinical experience. DPP-4 inhibitors work by blocking the action of DPP-4, an enzyme which destroys the hormone incretin. Incretins help the body produce more insulin only when it is needed and reduce the amount of glucose being produced by the liver when it is not needed. These hormones are released throughout the day and levels are increased at meal times.

Medications in the DPP-4 inhibitor family

Table 2:

Generic Name	Brand or trade name
Sitagliptin	Januvia
Sitagliptin + Metformin	Janumet
Vildagliptin	Galvus
Vildagliptin + Metformin	Eucreas
Saxagliptin	Onglyza

"For treating elderly T2DM patients, DPP-4 inhibitors were more expensive and less effective, i.e. a dominated strategy, than the metformin monotherapy. [14] " Another study on cost effectiveneness of DPP4 by Jinsong et al found that, in patients with type 2 diabetes who do not achieve glycemic targets with antidiabetic monotherapy, DPP-4 inhibitors as add-on treatment may represent a cost-effective option compared with sulfonylureas and insulin. However, high-quality cost-effectiveness analyses that utilize long-term follow-up data and have no conflicts of interest are still needed. [15]

Summary of the antidiabetic drugs

It is evident that metformin is the most cost effective drug as compared to all other antidiabetics as a montherapy. However more cost effectiveness is achieved when metformin is in combination therapy. The most expensive monotherapy is Sitaglpitin as well as less effective.

B. Laboratory Charges.

The following are the common tests for a diabetic patient which should be done monthly except for HBA1c. However these tests increase due to complications later on.

a. **HBA1c (Glycated Haemoglobin**) - This blood test indicates your average blood sugar level for the past two to three months. It measures the percentage of blood sugar attached to hemoglobin, the oxygen-carrying protein in red blood cells. The higher your blood sugar levels, the more hemoglobin you'll have with sugar attached. An A1C level of 6.5 percent or higher on two separate tests indicates that you have diabetes. An A1C between 5.7 and 6.4 percent indicates prediabetes. Below 5.7 is considered normal.

b. **Random blood sugar test.** A blood sample will be taken at a random time. Regardless of when you last ate, a random blood sugar level of 200 milligrams per deciliter (mg/dl) — 11.1 millimoles per liter (mmol/L) — or higher suggests diabetes.

c. **Fasting blood sugar test.** A blood sample will be taken after an overnight fast. A fasting blood sugar level less than 100 mg/dL (5.6 mmol/L) is normal. A fasting blood sugar level from 100 to 125 mg/dl(5.6 to 6.9 mmol/L) is considered prediabetes. If it's 126 mg/dL (7 mmol/L) or higher on two separate tests, you have diabetes.

d. **Post parandial blood sugar** - A postprandial glucose test is a blood glucose test that determines the amount of a type of sugar, called glucose, in the blood after a meal. Glucose comes from carbohydrate foods. It is the main source of energy used by the body. Normally, blood glucose levels increase slightly after eating. Postprandial" sugars taken two hours after meals should be less than 140 mg/dl

Summary of laboratory charges of diabetes

Laboratory charges are part of medical costs incurred by patients. Studies show that the laboratory charges take up to 10% - 40% of total medical costs incurred by patients and cannot be avoided since patients need to monitor their sugar levels every once and again.

C. Physician Charges

These are the charges that patients pay in order to see a physician. These charges have been seen to consume at least 5 – 25 % of the total medical costs incurred by the patient. [11]These charges are varied from hospital to hospital and are inevitable unless in government hospitals in specific countries

D. Cost of complications

Diabetes Mellitus is a disease with numerous complications which when not treated will lead to death or reduced health in patients. Therefore along treatment of DM, the patients are faced with the task of treating the complications. This makes DM an expensive disease to treat. DM direct treatment costs increased with the presence and progression of chronic DM related complications. [16]

The following are the complications of dm

- **Heart and blood vessel disease.** Diabetes dramatically increases the risk of various cardiovascular problems, including coronary artery disease with chest pain (angina), heart attack, stroke, narrowing of arteries (atherosclerosis) and high blood pressure.
- **Nerve damage (neuropathy).** Excess sugar can injure the walls of the tiny blood vessels (capillaries) that nourish your nerves, especially in the legs. This can cause tingling, numbness, burning or pain that usually begins at the tips of the toes or fingers and gradually spreads upward. Poorly controlled blood sugar can eventually cause you to lose all sense of feeling in the affected limbs. Damage to the nerves that control digestion can cause problems with nausea, vomiting, diarrhea or constipation. For men, erectile dysfunction may be an issue.

- **Kidney damage (nephropathy).** The kidneys contain millions of tiny blood vessel clusters that filter waste from your blood. Diabetes can damage this delicate filtering system. Severe damage can lead to kidney failure or irreversible end-stage kidney disease, which often eventually requires dialysis or a kidney transplant.

- **Eye damage.** Diabetes can damage the blood vessels of the retina (diabetic retinopathy), potentially leading to blindness. Diabetes also increases the risk of other serious vision conditions, such as cataracts and glaucoma.

- **Foot damage.** Nerve damage in the feet or poor blood flow to the feet increases the risk of various foot complications. Left untreated, cuts and blisters can become serious infections, which may heal poorly. Severe damage might require toe, foot or leg amputation.

- **Hearing impairment.** Hearing problems are more common in people with diabetes.

- **Skin conditions.** Diabetes may leave you more susceptible to skin problems, including bacterial and fungal infections.

Summary of treating diabetic complications

On an average, diabetic patients with foot complications (19020 INR) and those who have presence of two complications (17633 INR) spent 4 times more and patients with chronic kidney disease (12690 INR), cardiovascular complications (13135 INR) and retinal complications (13922 INR) spent three times more than patients without any complications (4493 INR). The total median expenditure for the hospital admissions in the previous 2 years was significantly higher for patients with foot complications (150000 INR) and cardiovascular complications (200000 INR) and it was highest if they have presence of two complications (282500 INR) [17]

NEED

The demand for and the cost of health care are increasing in all countries as the improvement in and sophistication of health technologies. Cost of medicines are growing constantly as new medicines are marketed and are under patent law, preference of drug therapy over invasive therapy, discovering various off label uses of existing drugs and the irrational drug prescription.

Therefore the following are the need of pharmacoeconomic study:

1) Rising health expenditures have led to the necessity to find the optimal therapy at the lowest price
2) Numerous drug alternatives and empowered consumers also fuel the need for economic evaluations of pharmaceutical products
3) The increasing cost of healthcare products and services has become a great concern for patients, healthcare professionals, insurers, politicians and the public.
4) Healthcare resources are not easily accessible and affordable to many patients; therefore pharmacoeconomic evaluations play an important role in the allocation of these resources.
5) For the formulating of the formulary the pharmacoecomic knowledge is necessary for the pharmacist and physicians.
6) It is increasingly becoming important for health policy decision making. Its need is undeniable, especially in developing countries.

Pharmacoeconomics is an innovative method that aims to decrease health expenditures, whilst optimizing healthcare results.

METHODS OF PHARMACOECONOMICS

There are basically 4 categories or types of pharmacoeconomic studies. These are presented here in order of detail,

1. Cost-minimization analysis (CMA)
2. Cost-effectiveness analysis (CEA)
3. Cost-utility analysis (CUA)
4. Cost-benefit analysis (CBA)

1. COST MINIMIZATION ANALYSIS

This involves measuring only costs, usually only to the health service, and is applicable only where the outcomes are identical and need not be considered separately. An example would be prescribing a generic preparation instead of the brand leader (lower cost but same health outcomes).

2. COST EFFECTIVE ANALYSIS

Compares the cost of drugs and their benefits and the benefits are measured in terms of natural units e.g.(ulcers healed ,FBS reduced) and the cost is measured in terms of money. CEA is the most commonly applied form of economic analysis in the literature, and especially in drug therapy. It does not allow comparisons to be made between two totally different areas of medicine with different outcome. E.g. comparing cost and effectiveness of antidiabetics whose both effect is reduction of FBS.

3. COST UTILITY ANALYSIS

This is similar to cost effectiveness in that the costs are measured in money and there is a defined outcome. But here the outcome is a unit of utility (e.g. a QALY). Since this endpoint is not directly dependent on the disease state, CUA can in theory look at more than one area of medicine, e.g. cost per QALY of coronary artery bypass grafting versus cost per QALY for erythropoietin in renal disease.

4. COST BENEFIT ANALYSIS

Here, the benefit is measured as the associated economic benefit of an intervention (e.g. monetary value of returning a worker to employment earlier), and hence both costs and benefits are expressed in money. CBA may ignore many intangible but very important benefits not measurable in money terms, e.g. relief of anxiety. CBA may also seem to discriminate against those in whom a return to productive employment is unlikely, e.g. the elderly, or the unemployed.

E.g. Comparing cost and effectiveness of antidiabetics whose both effect is reduction of FBS.

COST EFFECTIVENESS STUDY

Cost-effectiveness analysis (CEA) is a form of economic analysis that compares the relative costs and outcomes (effects) of different courses of action. Cost-effectiveness analysis is distinct from **cost**–benefit analysis, which assigns a monetary value to the measure of effect. It is used to compare different drugs which have the same outcome. The cost and effectiveness of the drugs are compared and the cost effective drug is considered.

CEA is most useful when analysts face constraints which prevent them from conducting cost-benefit analysis. The most common constraint is the inability of analysts to monetize benefits. CEA is commonly used in healthcare, for example, where it is difficult to put a value on outcomes, but where outcomes themselves can be counted and compared, e.g. 'the number of lives saved'

CEA measures costs in a common monetary value (££) and the effectiveness of an option in terms of physical units. Because the two are incommensurable, they cannot be added or subtracted to obtain a single criterion measure. One can only compute the ratio of costs to effectiveness in the following ways:

$$\text{CE ratio} = C1/E1$$

$$\text{EC ratio} = E1/C1$$

Where: C1 = the cost of option 1 (in £); and E1 = the effectiveness of option 1 (in physical units).

ICER

The incremental cost-effectiveness ratio (ICER) is a statistic used in cost-effectiveness analysis to summarize the cost-effectiveness of a health care intervention. It is defined by the difference in cost between two possible interventions, divided by the difference in their effect.

ACER

The average cost-effectiveness ratio (ACER) is the ratio of the cost to benefit of an intervention without reference to a comparator.

Result of cost effectiveness analysis is expressed as an average cost effectiveness ratio (ACER) or as incremental cost effectiveness ratio (ICER).

ACER/ICER = healthcare cost divided by clinical outcome /benefit.

LITERATURE REVIEW

- **Ping et al in a study of economic impact of diabetes** 2010 surveyed that Global health expenditures to prevent and treat diabetes and its complications will total at least US dollar (USD) 376 billion in 2010. By 2030, this number will exceed some USD 490 billion. Expressed in International Dollars (ID), which correct for differences in purchasing power, the global expenditures on diabetes will be at least ID418 billion in 2010, and at least ID561 billion in 2030. An average of USD703 (ID878) per person will be spent on diabetes in 2010 globally. Expenditures spent on diabetes care are not evenly distributed across age and gender groups. More than three-quarters of the global expenditure in 2010 will be used for persons who are between 50 and 80 years of age. Also, more money is expected to be spent on diabetes care for women than for men.[18]

- **American diabetes association 2016 in the staggering costs of diabetes mellitus** in America had the following alarming findings that in Americans having diabetes $1 in $3 Medicare dollars is spent caring for people with DM. Diabetes and prediabetes cost in America $322 billion. 86 million Americans have prediabetes and 1$ in 5$ health care dollars is spent caring for people with diabetes. Today 3,835 Americans will be diagnosed with DM. today diabetes will cause 200 Americans to undergo an amputation, 136 to enter end stage kidney disease treatment and 1,795 to develop severe retinopathy that can lead to severe blindness. This is quite already very alarming and shows that something has to be done.

- **Jitendrah Singh, Economic burden of diabetes mellitus found that** The average expenditure per patient per year would be a minimum of INR 4,500 (approximately US $120). Therefore, the estimated annual cost of diabetes care would be approximately 180,000 million rupees.[5] In India, estimates suggest that 85–95% of all health care costs are borne by individuals and their families from household income. The lowest income groups bear the greatest burden, paying a larger proportion of household income toward diabetes care. Direct expenses consume 27–34% of household incomes of rural and urban poor people while the middle-to-high income groups in rural and urban areas consume 5.0–12.6% and 4.8–16.9%

of income respectively on diabetes care. Year-on-year increases in this proportion are greater in impoverished groups, worsening with duration of diabetes, presence of complications, hospitalization, surgical therapy and glycemic control requiring insulin .[2]

- **Ahmad et al, comparing knowledge of DM among rural and urban diabetics 2007** discovered that urban diabetic patients are more aware than rural diabetic patients about diabetes mellitus. Therefore the rural patients have an increased morbidity and mortality rate compared to urban patients due to lack of disease knowledge.[20]

- **David C Klonoff** in the study **the increasing incidence of Diabetes Mellitus in 21st century** determined the reason for the uprising pandemic is due to increased obesity in the USA. He said as many obesity cases were rising also diabetic cases were increasing. This he said could be due to increasing intake of fast foods.[21]

- **Sujatha** sought to find out why India has a rise in the chronic disease in her study **Prevalence of DM 2015 in India** and she came up with the following reasons : Genetic factors are among the greatest contributors to the rapid spread of this disease. On an average, Indians are four times more likely to develop diabetes than Europeans, based solely on genetic outlook. Cultural and social factors are no less important. The Indian diet is rich in carbohydrates and saturated fats. A typical Indian diet is has more calories and sugar than required by the body. This is the cause of obesity, which in turn leads to diabetes. Urban migration and change in lifestyle is another factor that must be considered in the study of diabetes in India. The younger generations are increasingly choosing a sedentary lifestyle. With rising standard of living comes the tendency to consume processed sugary foods. [22]

- **Giwa A et al** on **cost effectiveness analysis of antidiabetic therapy** sought to find out the cost effective therapies being utilized in the hospital and they came up with the following that Glibenclamide was the most cost effective monotherapy and Glibenclamide and metformin were the most cost effective combined therapy.[23]

- **D Limaye et al** on a **cost effectiveness study of antidiabetic drugs in Mumbai** studied the prescription pattern and found out that Glimepride and metformin were the most cost effective followed by metformin.[24]

- **Abdelaziz MSL et al** on **Pharmacoeconomic evaluation agents in Bangalore** did a cost effective analysis and a cost of illness study on diabetes mellitus treatment. They found out that treating DM is expensive and most patients paid 3000-8000 INR in treating DM during period of study and on the most cost effective drugs they found that the combination of metformin and Glimepride was the most cost effective combination.[11]

- **Ghalamreza Y. et al on prescription pattern study in T2DM in outpatients in Iran** studied the prescription pattern of DM and found out the following Out of the 1118 prescriptions of antidiabetic drugs studied, 424 (37.9%) were for women and 694(62.1%) were for men with mean age of 56.2±11 years. Oral antidiabetic drugs were prescribed for 777(69.5%) and 30.5% of patients received insulin. Biguanides were the most frequently prescribed drugs (61.7%) followed by sulfonylurea (59.9%), alpha-glucosidase inhibitors (4.5%), repaglinide (NovoNorm®) (2.7%) and thiazolidinediones (1.7%). Metformin 690 (61.7%) and glibenclamide 670 (59.9%) were the most frequently prescribed antidiabetic drug. In comparison between the monotherapy and combination they found out that About 46.9% of patients received monotherapy and a total of 594 (53.1%) patients were on combination therapy of 2 or more antidiabetic drugs. The Combination of glibenclamide plus metformin (41.5%) was the most commonly prescribed antidiabetic drug combination in diabetic outpatients. Most common prescribed drugs associated with DM were found to be antihypertensive/antianginal (65%) and lipid lowering drugs (33.3%). [25]

- **Nasir T et al** in a **study on medication adherence in DM and self management practices in Ethiopia** observed the diabetic patients and their medication adherence. He found out that Majority of the patients with type 2 diabetes in Ethiopia are managed by OHA monotherapy mainly glybenclamide and metformin. While the current prescribing strategy do not achieve glycemic control on majority of the patient. This is due to poor adherence with the prescribed drug regimen and poor knowledge and practice of successful self management. Therefore he attributed the lack of achieving glycemic control to medical non adherence. [26]

- **Ranjit U et al** on a study on **DM and its complications in India** did an elaborate study on the main complications diabetic patients had. He discovered that the increase of complications was the more cause of morbidity and mortality. Among the complications discussed he found out that more than 65% of patients with T2DM die of cardiovascular disease; of these, nearly 80% are attributable to coronary artery disease (CAD). The susceptibility of Asian Indian individuals to CAD is well known. Compared with white individuals, CAD tends to develop a decade or two earlier and triple vessel diseases is more common; mortality after an acute coronary event is also 40% higher in Asian Indian patients. The presence of T2DM seems to confer a 3–4 times higher risk of cardiovascular disease to Asian Indian individuals than to their white counterparts, even after adjusting for sex, age, smoking status, hypertension and obesity. He also had a finding on diabetic foot ulcer that Diabetic foot ulcers and infections are responsible for >30% of the hospitalizations related to diabetes mellitus. 25% of people with diabetes mellitus are estimated to develop a foot ulcer during their lifetime. Diabetic foot ulceration is also an expensive complication of diabetes mellitus, owing to both medical care and on account of time lost from work and loss of income and financial independence.[27]

- **Amandeep S et al** in a study of **drug utilization and pharmacoeconomics of antidiabetic drugs** found out the most cost effective antidiabetic drug utilized and they found out that Metformin was the most common OAD agent and insulin asparte was the most common injectable anti-diabetic drug prescribed in patients withT2DM. The newer anti-diabetic drugs sitagliptin and newer insulin analogues were also prescribed to a great extent. Overall, the prescribing trend was rational to a great extent and had improved since the earlier study in the same institute. The most cost-effective anti-diabetic therapy was combination therapy of glipizide and metformin.[28]

- **Gerald Ochieng** in a study done in Kenya about **comparative cost effectiveness of metformin therapy and metformin and DPP_4 combination therapy** discussed elaborately that the use of the newer drugs DPP_4 in a combination with metformin was quite cost effective as compared to using metformin as a single therapy. [10]

- **Pheil L et al** in a study on **what next after metformin?** Focused on the use of sulphonyl ureas. Adding sulphonylurea to metformin targeted both insulin resistance and insulin deficiency. Sulphonylurea was efficacious and cheaper than thiazolidinedione, dipeptidyl peptidase-4 inhibitor, glucagon-like peptide 1 analogue and insulin. The main side effect of sulphonylurea was hypoglycaemia but there was no effect on the body weight when combining with metformin. Fixed dose sulphonylurea/metformin was more efficacious at lower dose and reported to have fewer side effects with better adherence. Furthermore, fixed dose combination was cheaper than add-on therapy. In conclusion, sulphonylurea was feasible as the second line agent after metformin as the combination targeted on two pathways, efficacious, cost-effective and had long safety history. Fixed dose combination tablet could improve patient's adherence and offered an inexpensive and more efficacious option regardless of original or generic product as compared to add-on therapy. [12]

AIM AND OBJECTIVES

AIM

To determine the pharmacoeconomic burden and the oral cost effective therapy in the management of Type 2 Diabetes Mellitus

OBJECTIVES

- To document the prescription given to the patients.
- To assess the cost of oral anti diabetic drugs.
- To evaluate the effectiveness of the prescribed drugs.
- To determine the cost effectiveness of the oral hypoglycemic agents given.
- To calculate the direct medical costs incurred by the ambulatory diabetic patients in one month.
- To come up with the total cost of illness incurred by all the patients in one month.

METHODOLOGY

Study design:-

Retrospective – Pharmacoeconomic study- cost effective analysis

Study site:-

This retrospective – cost effective study was carried at the teaching hospital of PSG Medical Sciences and Research Institute, Coimbatore. This is a multispecialty 1000 bedded tertiary care hospital located in south region of Tamilnadu.

Study population:

Patients files from January to June 2016 who have Type 2 diabetes mellitus and are taking oral antidiabetic drugs.

Population size:

210 patients who suited the inclusion criteria were selected for the study.

Study period:

Study was carried out for the period of 6 months from October 2016 to March 2017.

Study Approval:

The protocol of the study was submitted to the Institutional Human Ethics Committee of our study hospital. The study was approved with the proposal number of 16/340 by the committee.

Data source:

Patients files from the Medical Record Department.

Patients Selection:

Inclusion Criteria –

- Age: any age
- Gender: male and female
- Patients with type 2 DM
- Patients on oral hypoglycemic drugs
- Patients who came back for review

Exclusion criteria:

- Type 1 DM
- Patients with type 2 DM but are on insulin
- Patients who are severely ill
- Pregnant and lactating patients

STUDY PROCEDURE:

- Study was selected after much analysis of the diseases and the decision was made after much consideration.

- In conjunction with my guide, I have selected the study on Pharmacoeconomic evaluation of oral antidiabetic and before proposing the study to ethical committee, I have done preliminary literature survey to design the data collection form.

- The study protocol was prepared and submitted in advance to the Institutional Human Ethics Committee (IHEC) for approval. The protocol was approved by the IHEC in the month of October 2016. This was then intimated to the Professors, Head of department of laboratory and Medical record department.

- The study was commenced on the month of October 2016, in the MRD of PS G Hospitals, Coimbatore. The patients files were studied carefully and the data collected in the data collection form.

- The collected files were screened for their demographic profiles which included the patients' age, sex, complications, laboratory investigations, drugs prescribed and the charges of the laboratory, physician charges and the complication charges.

- The charges of the laboratory investigations were acquired from the microbiology and pathology departments and the cost of drugs were acquired from HIS and the charges of physician were acquired from the patients' files.

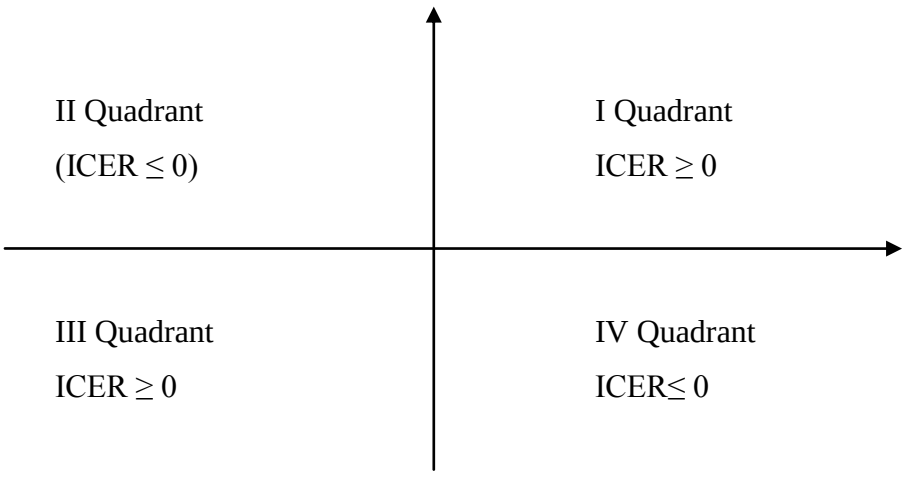
- The effect of the drugs was determined by calculation the p value of both the monotherapy and combination therapy using FBS as the unit of comparison.
- Later the cost effective therapy was determined by calculating the ICER and ACER and the cost effective monotherapy and combination therapy was determined.

- The total cost of illness was determined by totaling the charge incurred by the drugs, laboratory investigations, the physician charges and the charges of the complication.

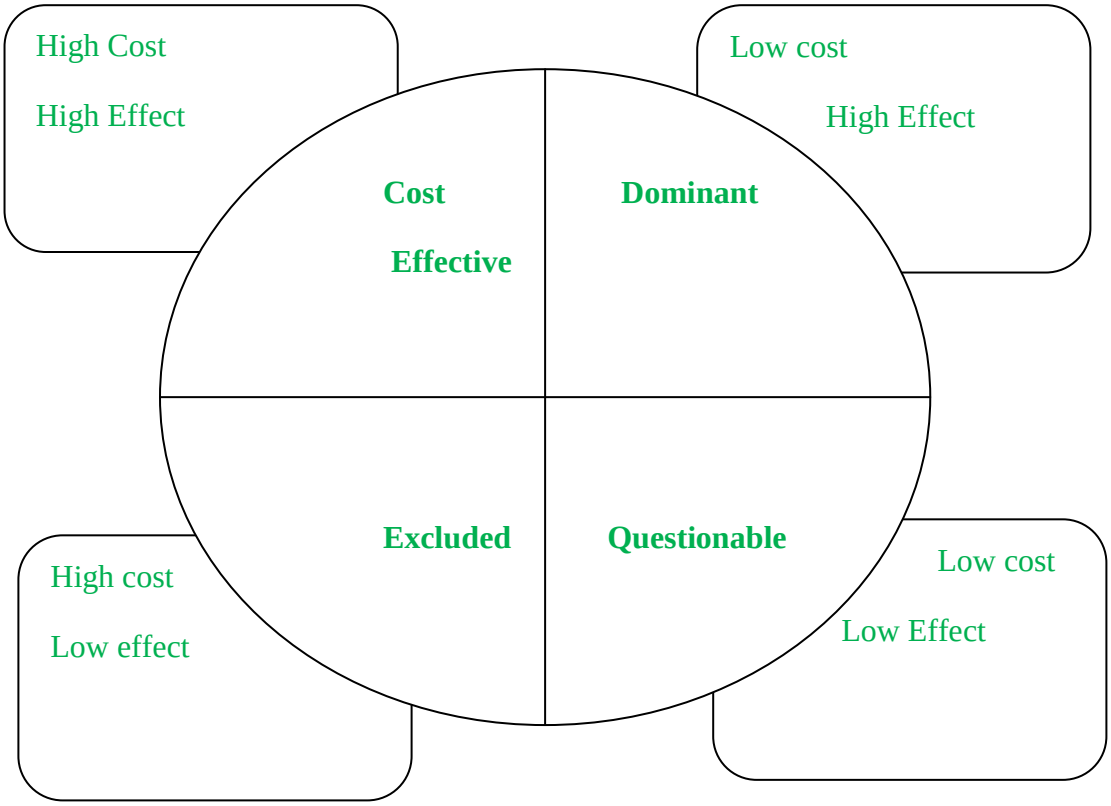
Outcome Measure: Incremental Cost Effective Ratio (ICER)

ICER = (Cost of X – Cost of Y)/ (Effect of X – Effect of Y)

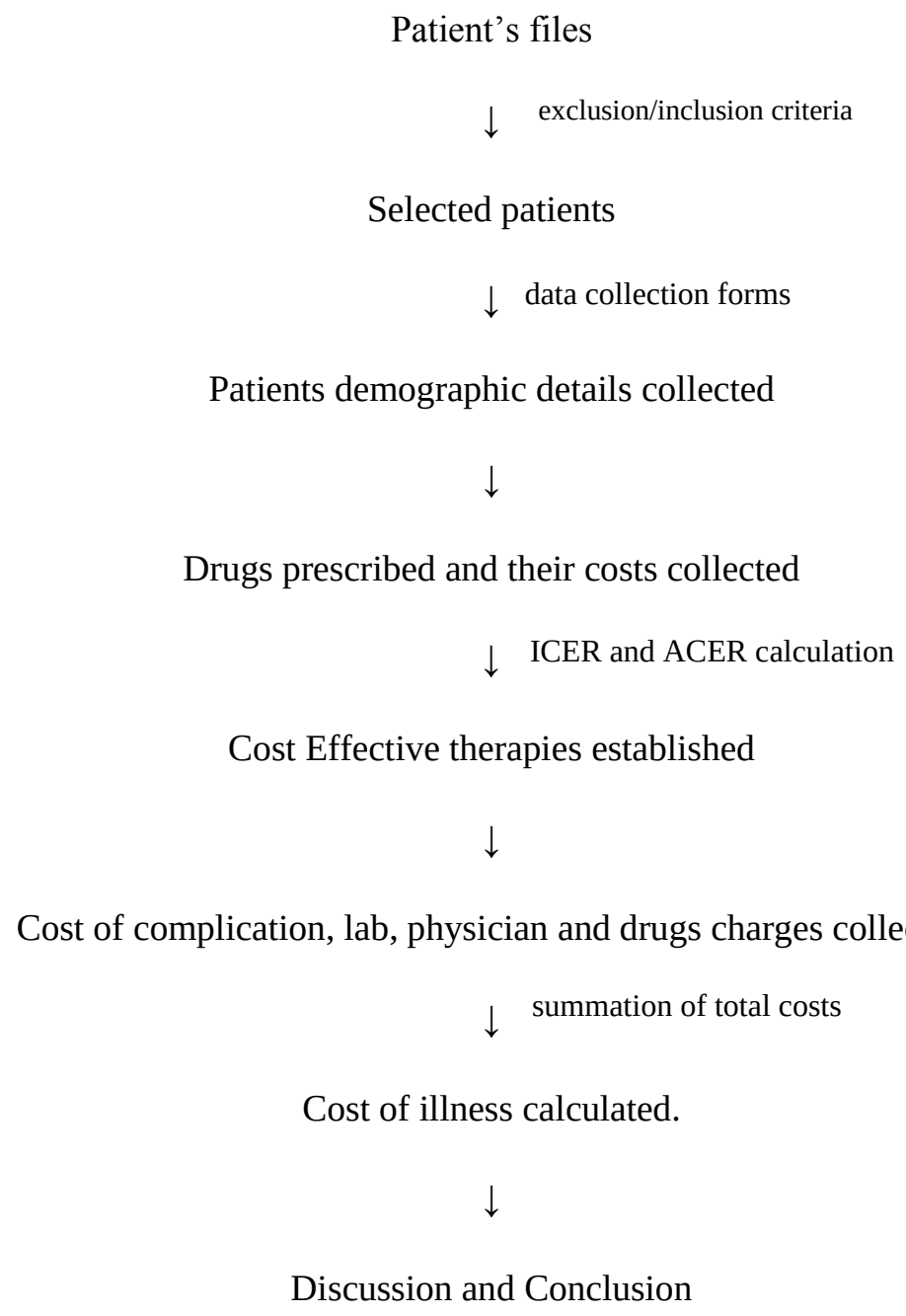
Data Interpretation: ICER Quadrant plane



Data Report: ICER Decision Matrix



FLOW CHART


Patient's files
exclusion/inclusion criteria
Selected patients
data collection forms
Patients demographic details collected
Drugs prescribed and their costs collected
ICER and ACER calculation
Cost Effective therapies established
Cost of complication, lab, physician and drugs charges collected
summation of total costs
Cost of illness calculated.
Discussion and Conclusion

RESULTS

Table No 3: Age wise distribution of Diabetic patients

Age in years	No of patients(n=210)	Percentage
30-40	11	5.2%
40-50	11	5.2%
50-60	62	29.5%
60-70	90	42.85%
70-80	34	16.19%
80-90	2	0.95%

Figure No 1: Age wise distribution of diabetic patients

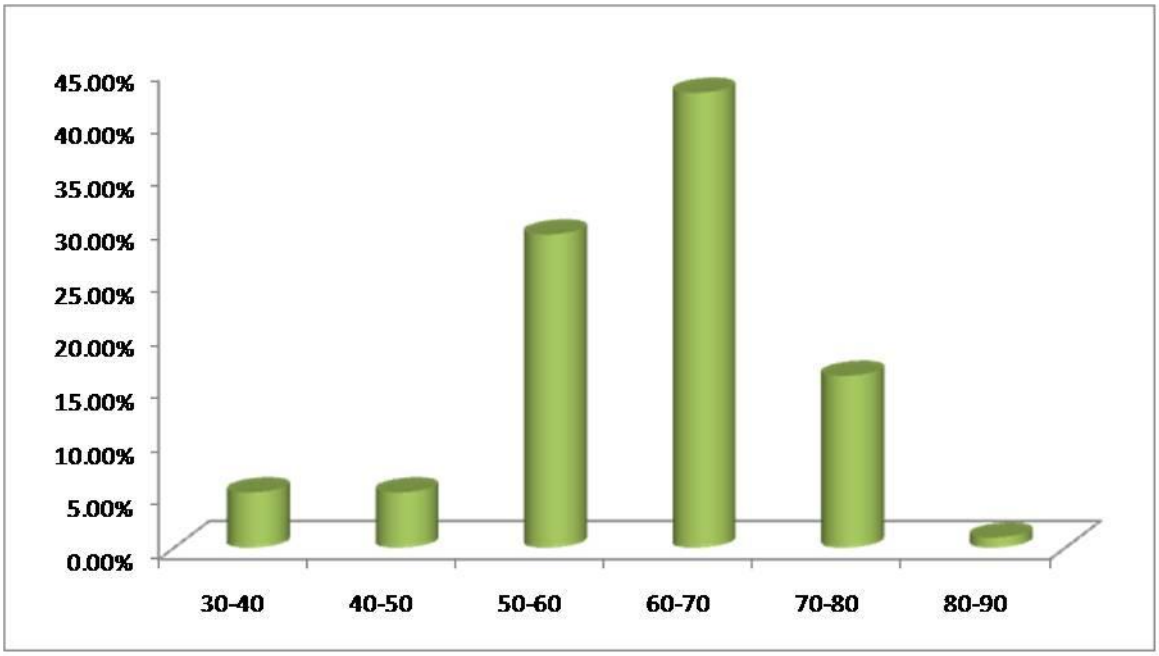


Table 4: Gender wise distribution

GENDER	**No of patients (n=210)**	**Percentage**
Male	126	60
Female	84	40

Figure 2: Gender wise distribution

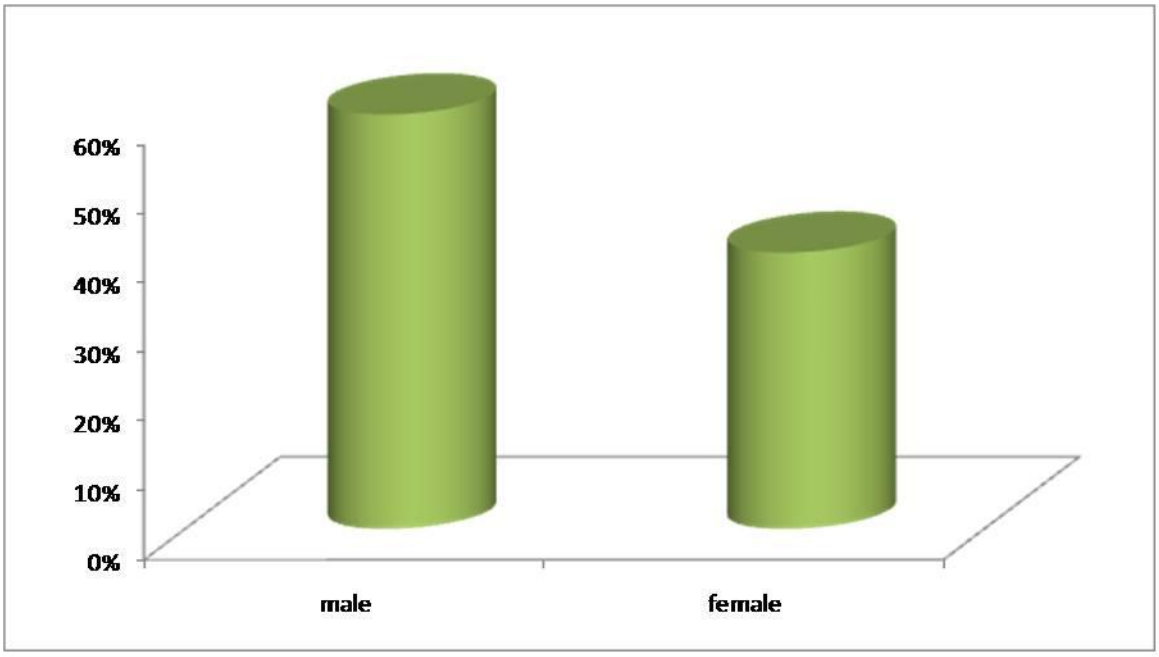


Table No 5: Co-morbidities of Diabetes Mellitus

Co- morbidities	No of patients (n=210)	Percentage
SHT	100	47%
FOOT ULCER	33	15%
DLP	24	11.4%
ACS	20	9.5%
UTI	11	5.2%
COPD	15	7.14%
OTHERS	7	3.33%

Figure No 3: Co-morbidities of Diabetes Mellitus

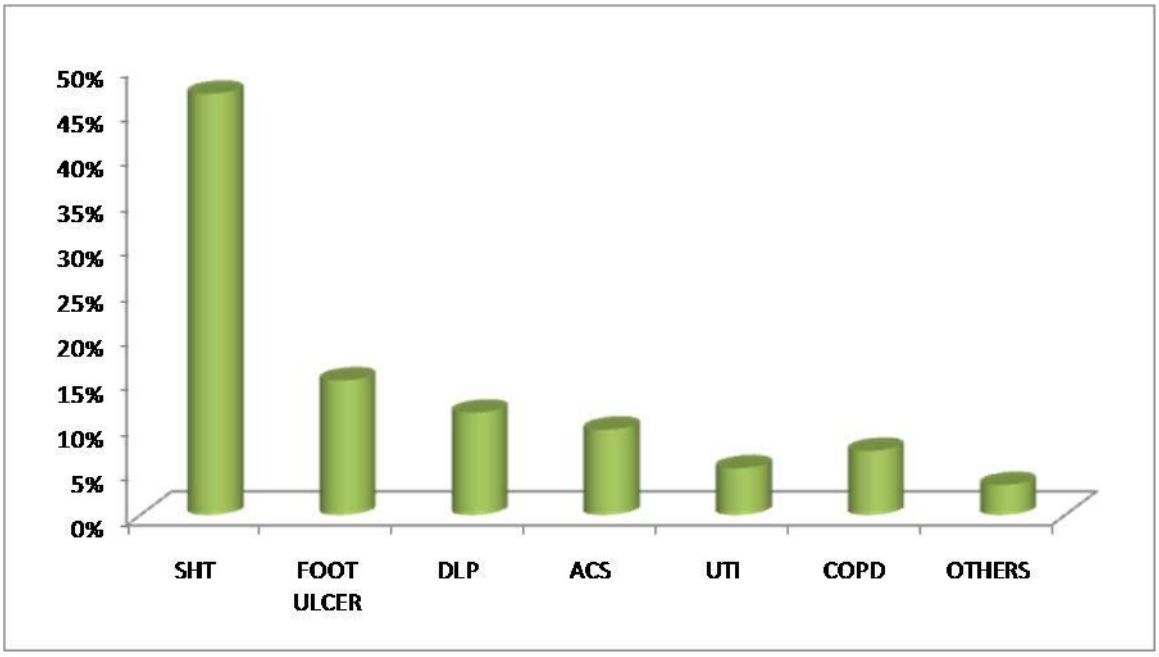


Table No 6: Social History of Diabetic Mellitus Patients

Social History	No of patients (n=210)	Percentage
Alcoholic	91	43%
Non alcoholic	119	57%
Smoker	88	41.9%
Non smokers	122	58.09%
Both alcoholic and smokers	60	28.57%

Figure No 4: Social History of DM patients

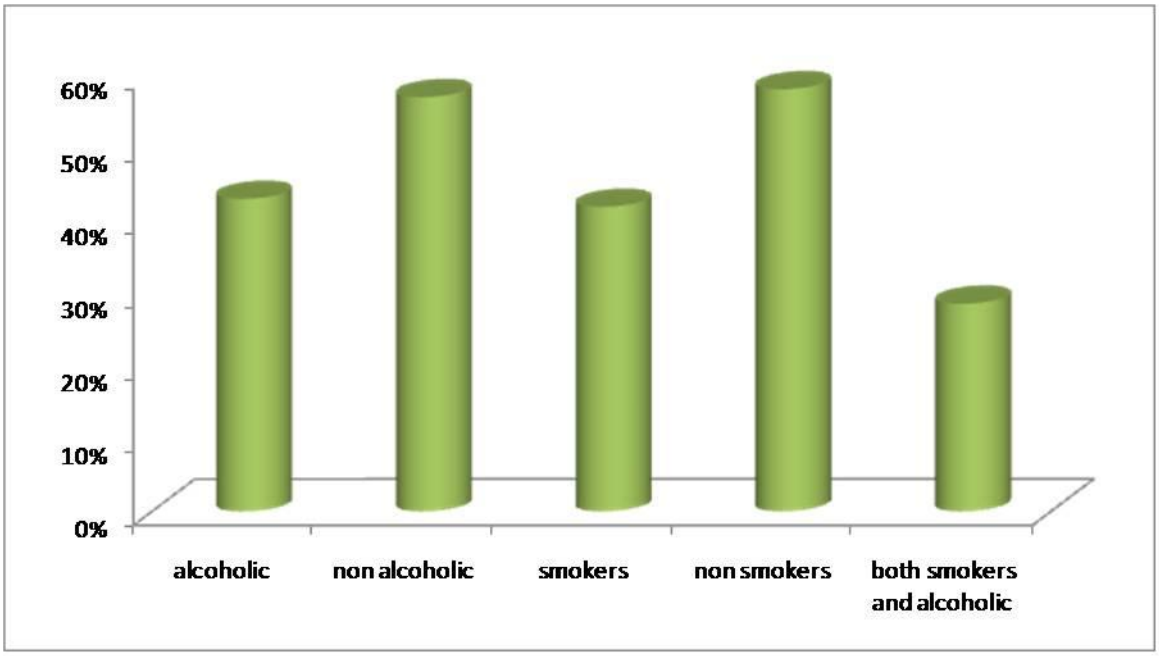


Table No 7: Classification of oral antidiabetic drugs. (Monotherapy)

Class of drugs	No of patients	Percentage
Biguanides	47	22%
Sulphonyl ureas	23	10.9%
Meglitinides	5	2.38%
Alpha glucosidase inhibitors	2	0.95%
Thiazolinediones	0	0%
DPP4 inhibitors	5	2.38%

Figure No 5: Classification of oral antidiabetic therapy (monotherapy)

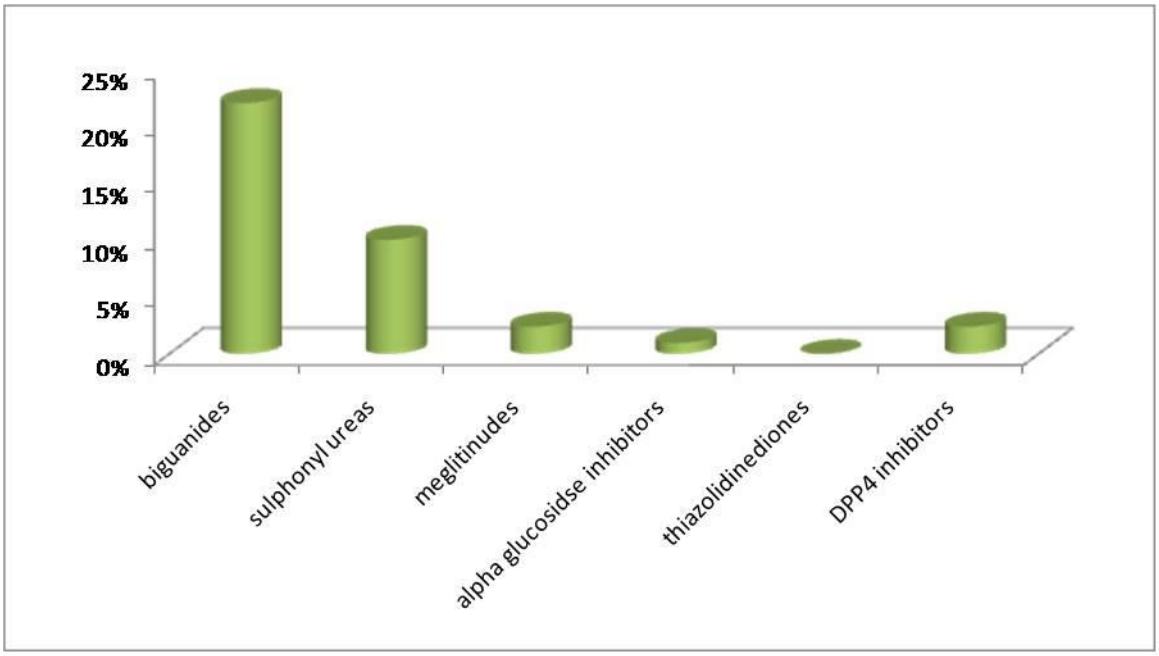


Table No 8: Percentage of oral antidiabetics drugs (monotherapy)

Brand Name	Generic Name	No of patients taking	Percentage of patients
Glycomet	Metformin	47	22.3%
Glycinorm	Glicazide	18	8.57%
Gluconorm	Repaglinide	5	2.38%
Amaryl	Glimepride	5	2.38%

Figure No 6: Percentage of oral antidiabetic drugs (monotherapy)

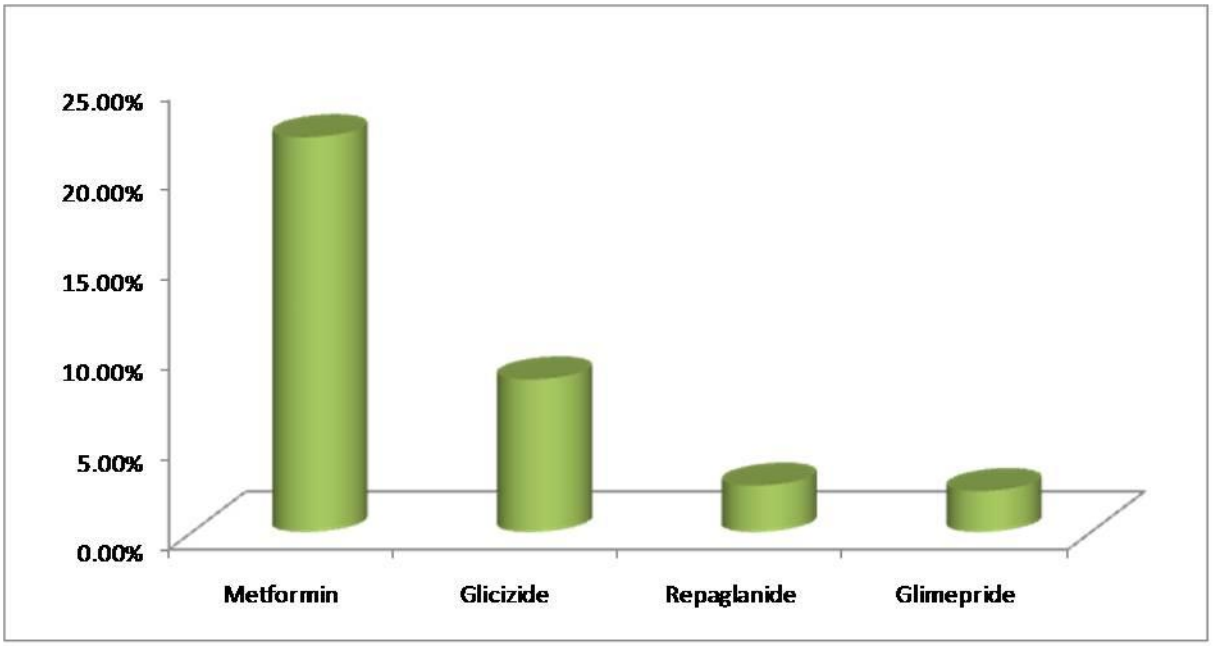


Table No 9: percentage of oral antidiabetic drugs (combination therapy)

a. Combinations with biguanides and sulphonyl ureas

Drugs names	No of patients	Percentage
Gemer (Glimepride + metformin)	3	1.42%
Glycomet + Gemer (Glimepride + metformin)	4	1.89%
Glycomet +Dianorm (metformin + Glicizide)	10	4.74%
Glyciphage + semiglynase (Glipizide)	5	2.37%
Glimisave + Glycomet	6	2.8%
Glycomet + Reclimet (metformin + Glicizide)	3	1.42%
Glipizide + metformin	9	4.27%
Glycomet +glimepride	11	5.22%
Glycomet + glycinorm	8	3.79%
Total	**59**	**28.09%**

b. Combinations of sulphonyl ureas and DPP4 inhibitors

Drug names	No of patients	percentage
Glycinorm + Galvus (vidagliptin)	3	1.36%
Glimepride + sitagliptin	15	6.81%
Glycinorm +galvusmet	4	1.82%
Total	**22**	**10.38%**

C. **Combination of biguanides and DPP4 inhibitors**.

Drug names	**No of patients**	**Percentage**
Janumet (metformin + sitagliptin)	2	**0.568%**
Galvusmet (Vidagliptin+metformin)	1	0.24%
Galvus (vidagliptin) + Glycomet	3	0.85%
Total	**6**	**1.42%**

d. Combination of three drugs

Drug names	No of patients	Percentage
Gemer(Glimepride + metformin) + Gluconorm (repaglanide)	9	4.28%
Glucobay (acarbose) + Glicizide + Janumet (sitagliptin +metformin)	3	1.42%
Reclimet (metformin + Glicizide)+ istamet (janumet)	4	1.90%
Janumet (siatgliptin + metformin) + Glimepride	6	2.85%
Total	**22**	**10.47%**

e. Combination of alpha glucosidase inhibitors and other drugs

Drug names	No of patients	Percentage
Glycomet + Glucobay (acarbose)	7	3.33%
Gemer + Glucobay	4	1.90%
Glicizid + volgbose	6	2.86%
Glycinorm + Glucobay	6	2.86%
Total	23	10.95%

Table No 10: percentage of combined oral antidiabetic therapy between classes

Class of drugs	No of patients	Percentage
Biguanide + sulphonyl ureas	59	28.09%
Sulphonyl ureas + DPP4 inhibtors	22	10.38%
biguanides + DPP4 inhibitors	3	1.425
alpha glucosidase inhibitors + others	22	10.95%
Combination of three drugs	23	10.74%

Figure No 7: percentage of combined oral antidiabetic therapy (classes)

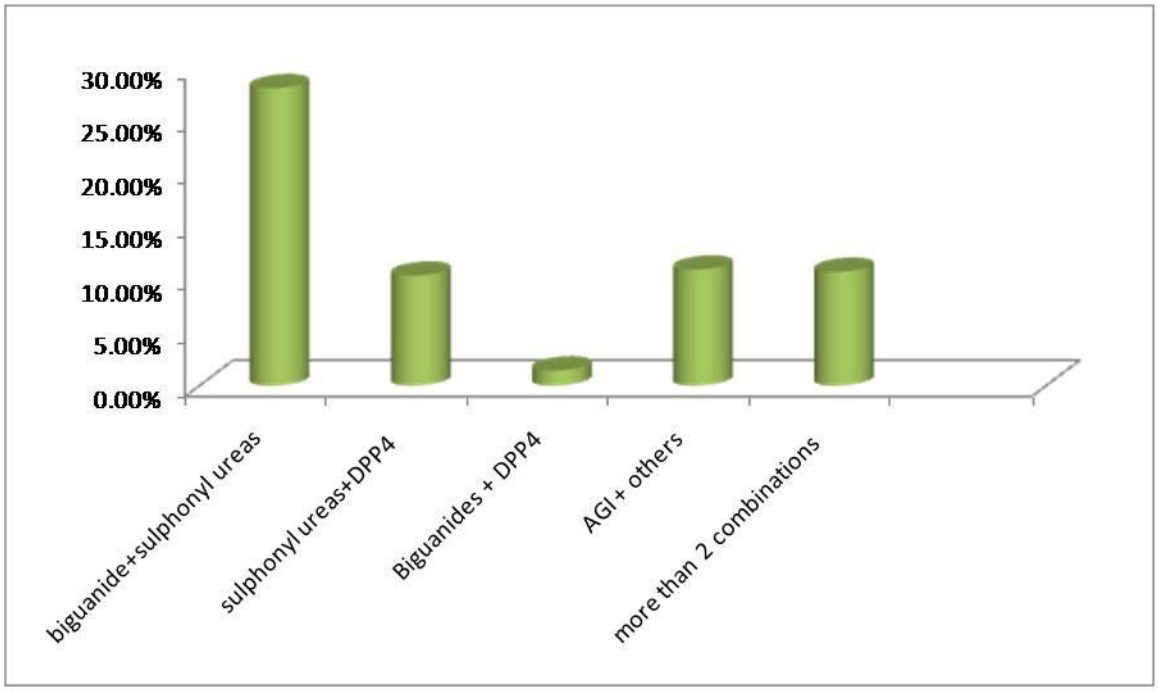


Table No 11: Management of complications of type 2 DM

Name of complication	Names of drugs given	No of patients	Percentage of patients
SHT	T cardace (Ramipril)	28	28%
N=100	T Telma (Telmasartan)	19	19%
	T amlodipine	10	10%
	T Repace (lorsatan)	15	15%
	T Lasix (furosemide)	10	10%
	T Hipril (lisinopril)	15	15%
	T Doxasazin	3	3%
Foot ulcer	Pregablin	**2**5	75%
	Neurobion forte	10	30%
N= 33	Ultracet	15	45%
	T Dalacin (clindamycin)	30	90%
Dyslipedemia	T Aztor (artovastatin)	14	70%
N= 24	T Rosuvas (Rosuvastatin)	6	30%
ACS	T ecosprin	20	100%
N= 20	T Storvas	14	70%
	T Clopilet	20	100%
UTI	T Levoflox	4	57%
N= 11	T Nitofurantoin	7	63.6%
COPD	T Montek LC	7	46%
N=15	Doxophylline	11	73.3%
	C .Mucinac	3	20%

Figure No 8: Management of SHT in Diabetic patients

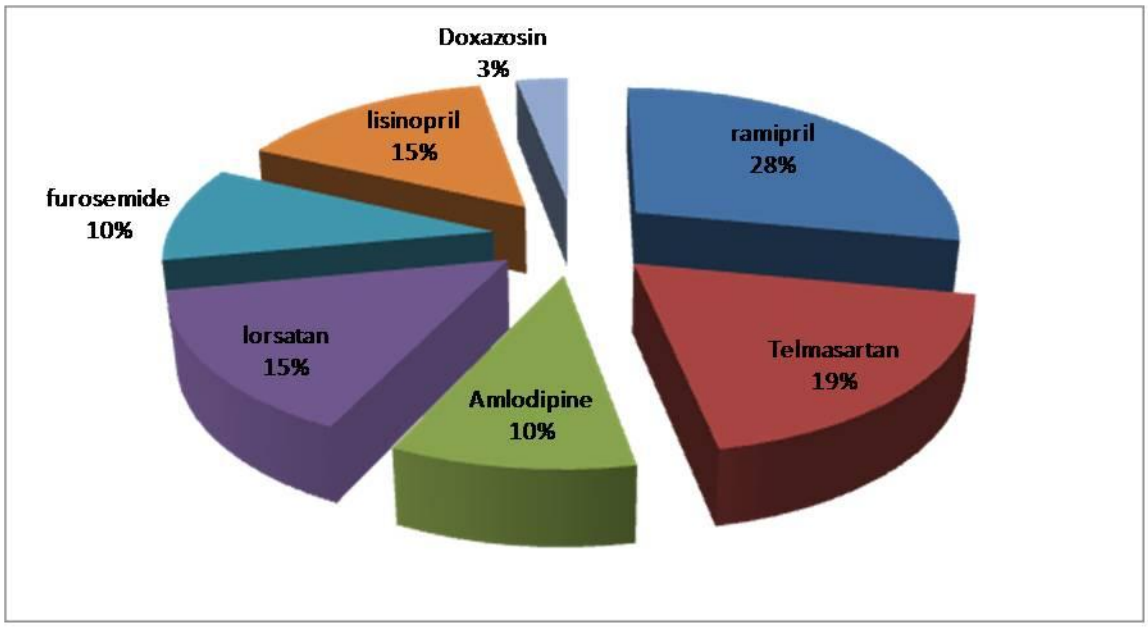


Figure no 9: Management of diabetic Foot ulcer

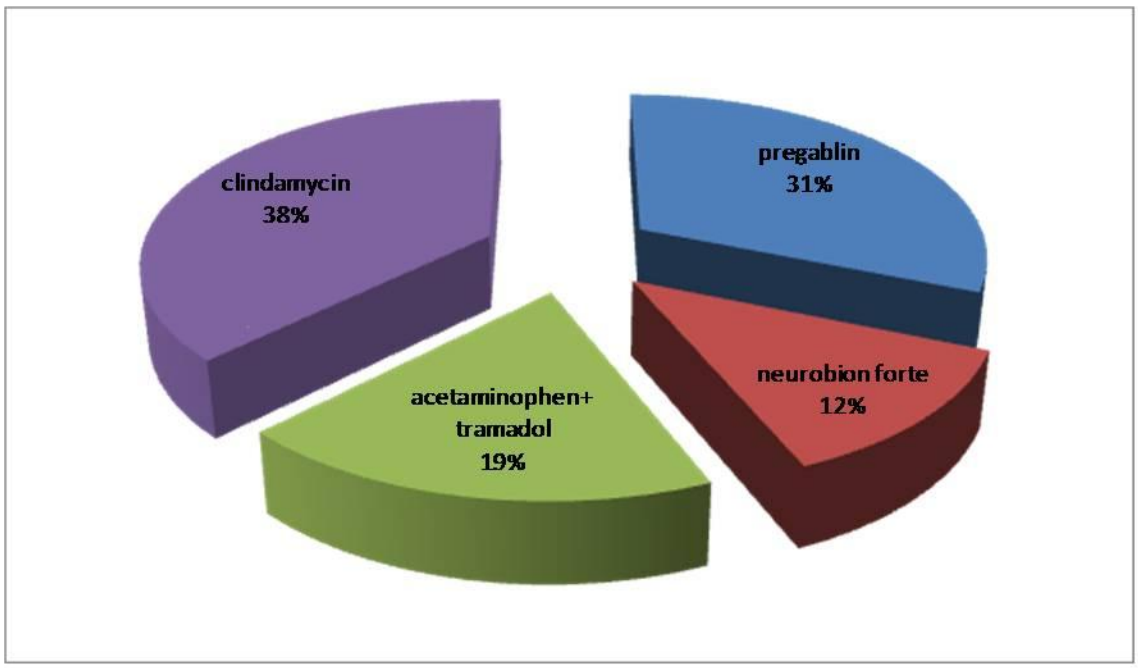


Figure No 10: Management of Dyslipedemia

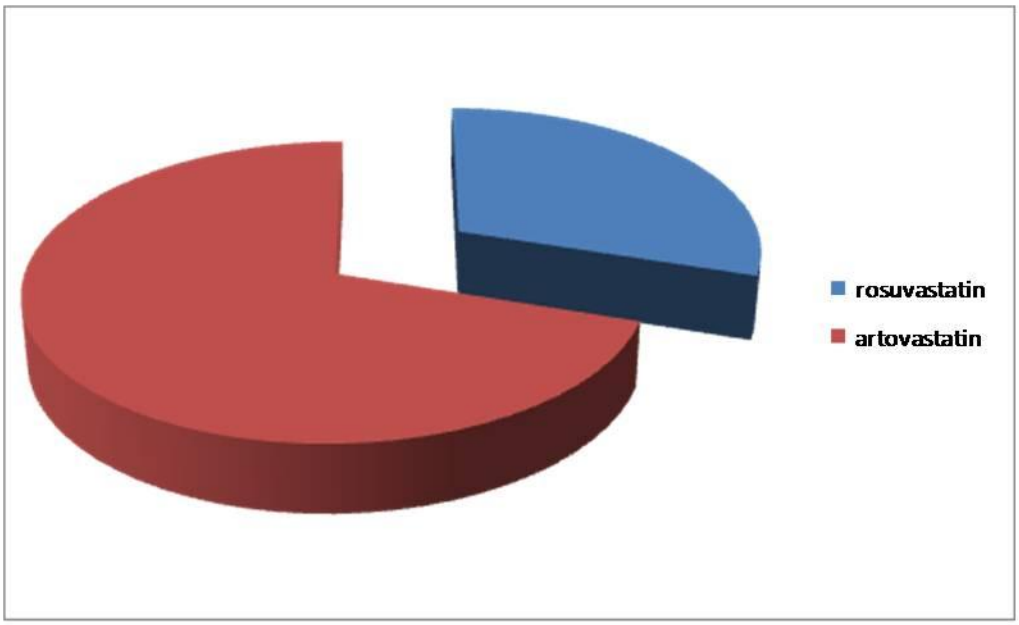


FIGURE NO 11: Management of acute coronary syndrome

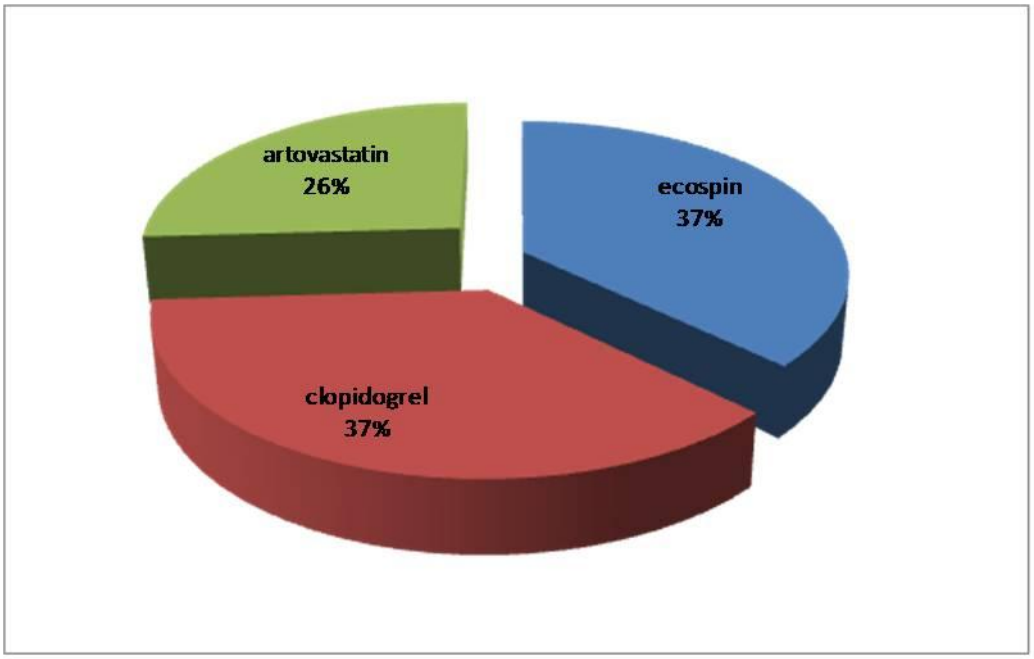


Table No 12: cost of oral antidiabetic drugs

Name of drug	Cost of single drug in Rs	Cost of drug in a month
Metformin	0.89	90
Glimepride	3.15	189
Glycinorm	2.66	160.73
Gluconorm	2.8	168
Janumet	12.63	758
Gemer	4.80	328
Amaryl	6.08	365
Galvusmet	3.58	215
Gemer + glycomet	6.30	372
Glycomet + dianorm	4.63	300
Glycinorm + Galvus	25.47	780
Glyciphage + semiglynase	10.20	208
Glimisave + glycomet	4.78	210
Galvus + Glycomet	22.08	1397
Gemer + Gluconorm	7.92	356
Glycomet + Reclimet	8.12	285
Glipizide + Metformin	4.78	1225
Glimipride + Sitagliptin	25.47	408
Glycomet + Glimepride	3.98	406
Glucobay+ Glicizide+ Janumet	293.27	737
Glycomet + Glucobay	9.24	279
Gemer + Glucobay	11.67	936
Glicizid + Volix	9.99	800
Reclimet + Istamet	348.53	892
Glycinorm + Galvusmet	214.84	825
Glycinorm + Glucobay	12.05	342
Janumet + Glycinorm	288.82	1490

Table No 13: Cost and FBS reduction of oral antidiabetics (monotherapy)

	Cost of single drug	Cost per month	Avg FBS reduced
Metformin	1.5	90	42.03mg/dl
Glicizide	3.15	160.73	22.26mg/dl
Repaglanide	2.26	168	7.33mg/dl
Glimepride	6.08	365	19.00mg/dl

Figure No 12: cost and FBS reduction of oral antidiabetics (monotherapy) per month

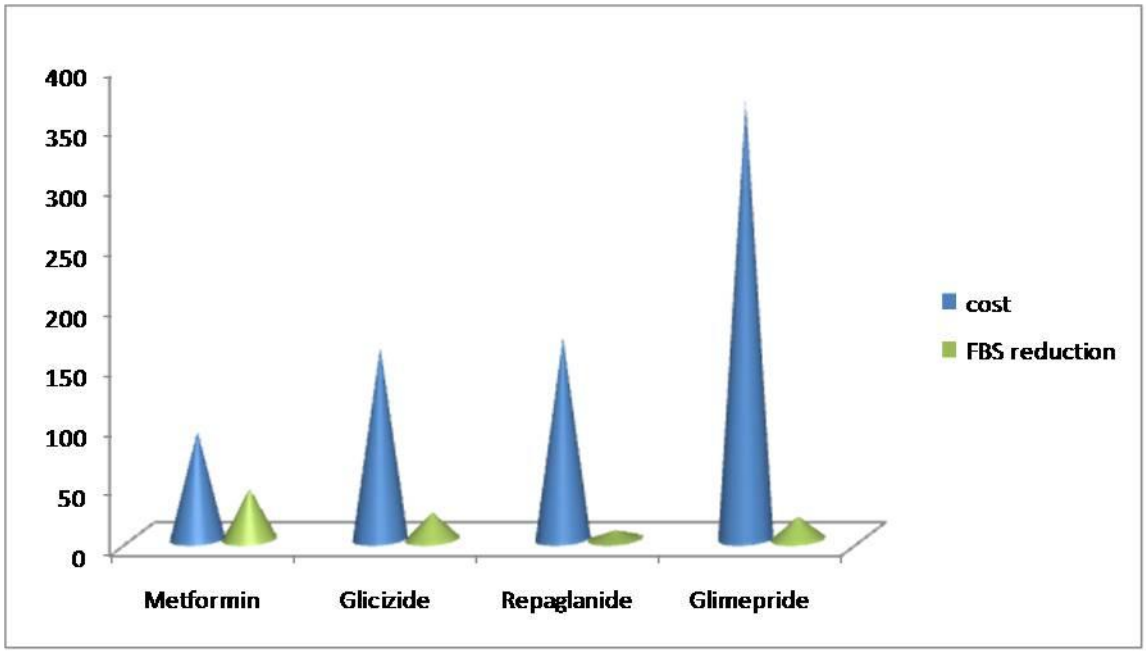


Table No 14: Cost and FBS reduction of oral antidiabetic drugs (combination therapy)

Category	Generic name	Cost in one month	AVG FBS reduction
1. Glimepride + metformin	a. Gemer	328	36 mg/dl
	b. Glycomet + Gemer	372	56.50 mg/dl
	c. Glycomet + Glimepride	406	47.90 mg/dl
2. Glicizide + metformin	a. Glycomet+ Dianorm	300	18.30 mg/dl
	b. Glimisave + Metformin	210	44.83 mg/dl
	c. Glycipahge + semiglnase	208	19.60 mg/dl
	d. Glycomet + Reclimet	285	36.66 mg/dl
	e. Glycomet + Glycinorm	270	80.37 mg/dl

Figure No 13: Cost and FBS reduction of oral hypoglcemic drugs (biguanide and sulphonyl ureas)

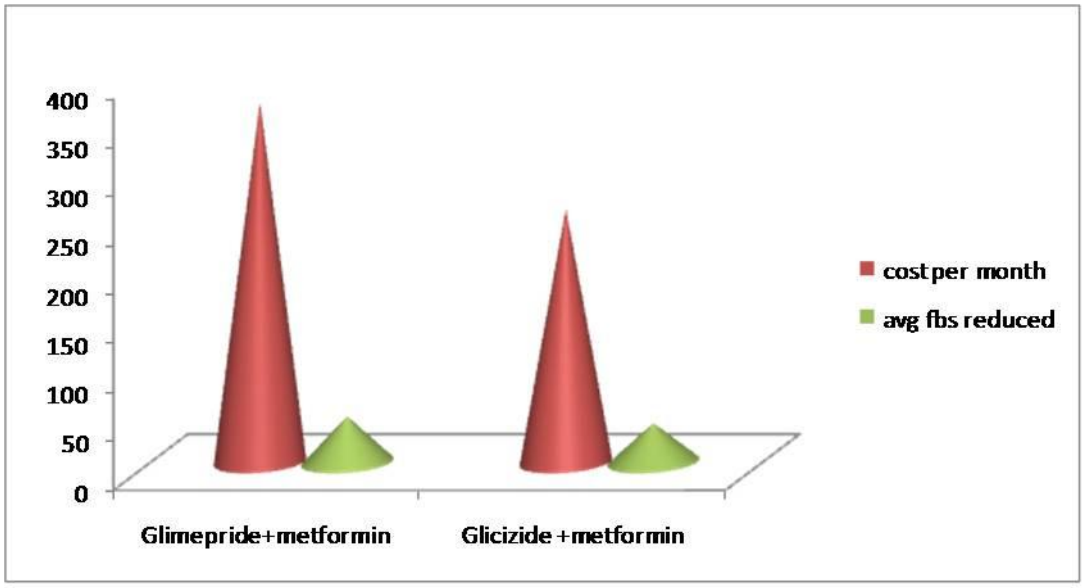


Table No 15: cost and FBS reduction of oral hypoglycemic drugs (DPP4 combinations)

category	Brand name	Generic name	Cost in a month	Avg FBS reduced Mg/dl
Dpp4 with biguanides	a. Janumet	a. sitagliptin +metformin	758	32
	b. Galvusmet	b. vidagliptin+ metformin	215	56.50
	c. Galvus + Glcomet	c. vidalgliptin + Metformin	210	39.66
		d. average	394.3	42.72mg/dl
DPP4 with sulphonyl ureas	a. Glycinorm+ Glavus	Glicizide+ vidagliptin	780	25.66
	b. Glimepride+sitagliptin	Glimepride + sitagliptin	408	12.60
	c. Glycoemt + Galvus	Glicizde + Vidagliptin	825	67.50
		average	671	35.25 mg/dl

Figure No 14: cost and FBS reduction of oral antidiabetic drugs (DPP4 combinations)

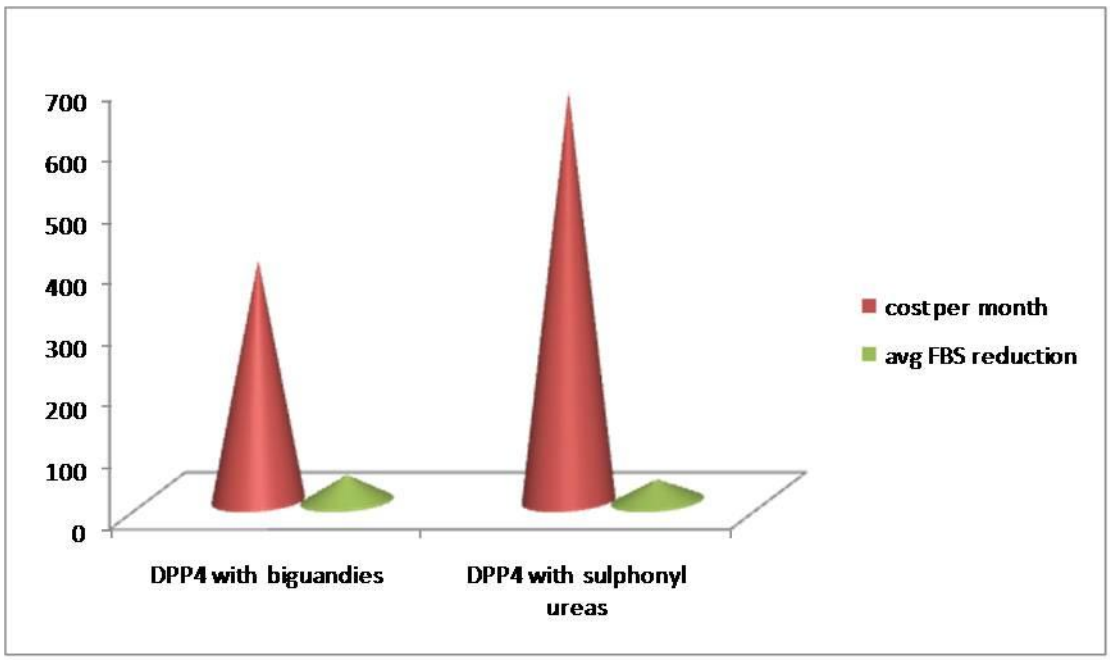


Table No 16: cost and FBs reduction of oral antidiabetics (alpha glucosidase inhibitors combinations)

Brand name	Generic name	Cost per month	AVG FBS reduction
Glycomet+ Glucobay	**Metfo**rmin + Acarbose	279	78mg/dl
Gemer + Glucobay	**Glime**pride +metformin + acarbose	936	75.50mg/dl
Glicizide + voligbose	**Glici**zide + voglibose	800	65.16mg/dl
Gl**y**cinorm + Glucobay	Glicizide + Acarbose	342	89.50mg/dl

Figure No 15: cost and FBS reduction of oral antidiabetic drugs (alpha glucosidase inhibitors combinations)

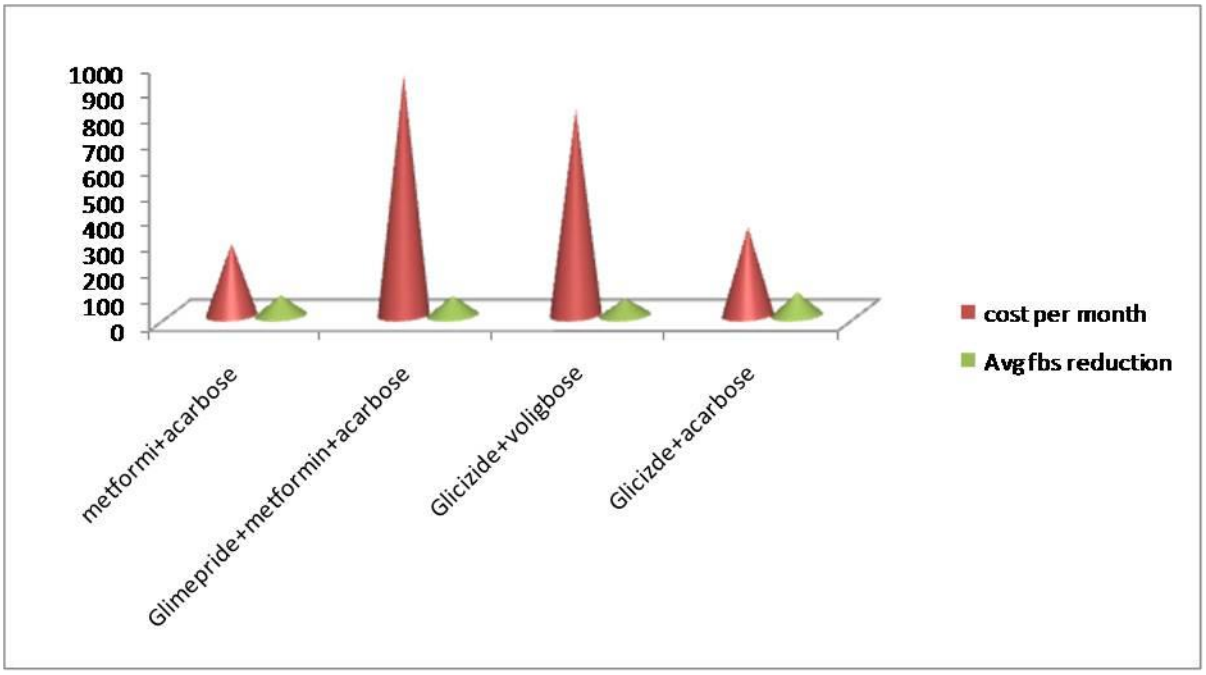


Table No 17: classification of lab investigations for diabetic patients

Name of lab investigation	Price of lab investigation	No of patients n=210	Percentage of patients
FBS	80	210	100%
RBS	80	102	48%
PPBS	80	177	84.2%
HBA1c	600	120	57.14%

Figure No 16: classification of lab investigations for diabetic patients

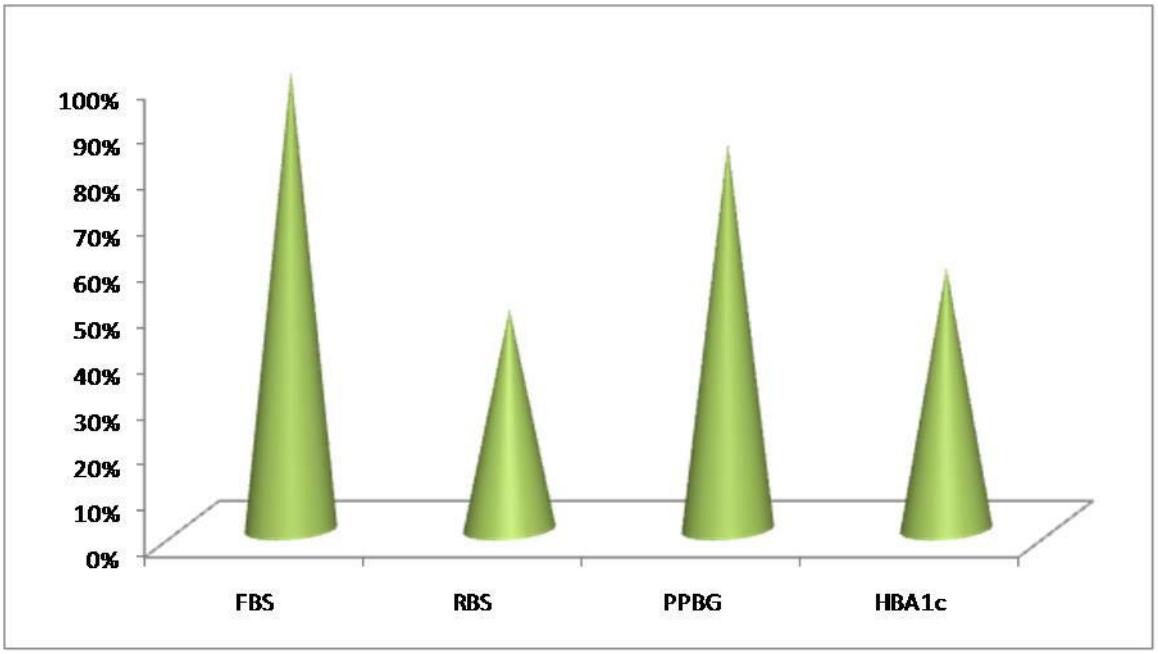


Table No 18: Effectiveness of oral antidiabetic drugs

Brand name	Generic name	FBS before therapy	FBS after therapy	Mean FBS reduction (mg/dl)	P value (before and after FBS)
Monotherapy					
Glycomet	Metformin	185.87	140.71	42.03	0.001**
Glycinorm	Glicizide	155.8	140.30	22.26	0.015
Gluconorm	Repaglanide	114	106.6	7.33	0.303
Amaryl	Glimepride	126.33	107.33	19.00	0.228
Combianation	**Therapy**				
Gemer	Glimepride + metformin	187	157	36.00	0.113
Glycomet + Gemer	Glimepride + metformin	199	142.5	56.50	0.058
Glycomet +Dianorm	Metformin + Glicizide	102	97	18.30	0.001**
Glyciphage + semiglynase	Metformin+ Glipizide	131	111.4	19.60	0.001**
Glimisave + Glycomet	Glimepride + Metformin	157.8	113	44.83	0.000***
Glycomet + Reclimet	Metformin + glicizide	224.67	188	36.66	0.053
Glipizide + metformin	Glipizide + metformin	133.89	116.33	17.55	0.000***
Glycomet +glimepride	Metformin + glimepride	220.63	172.92	47.90	0.000***
Glycomet + glycinorm	Metformin +glicizide	188	107	80.37	0.000***

Brand name	Generic name	FBS before therapy	FBS after therapy	Mean FBS reduction (mg/dl)	P value (before and after FBS)
DPP4 combinations					
Glycinorm + Galvus	Glicizide + vidagliptin	143	123	25.66	0.000***
Glimepride + sitagliptin	Glimepride +sitagliptin	116	103.4	12.60	0.012*
Glycinorm +galvusmet	Glicizide + Vidagliptin + Metformin	267	196	67.50	0.000***
Janumet	Metformin +sitagliptin	171	139	32.00	0.458
Galvusmet	Vidagliptin + Metformin	88	73	56.50	Not possible
Galvus + Glycomet	Vidagliptin+ Metformin	168.67	129	39.66	0.012*
Acarbose combinations					
Glycomet + Glucobay	Metformin+Acarbose	234.57	156.57	78.00	0.000***
Gemer + Glucobay	Glimepride+ metformin +acarbose	274	198.5	75.50	0.000***
Glicizid + volix	Glicizide+ Voligbose	236.17	171	65.16	0.001**
Glycinorm + Glucobay	Glicizide+ Acarbsoe	215	123	89.50	0.000***

Brand name	Generic name	FBS before therapy	FBS after therapy	Mean FBS reduction (mg/dl)	P value (before and after FBS)
More than two combinations					
Gemer+ Gluconorm	Glimepride+metformin+ Repaglinide	184.8	145	39.87	0.000***
Glucobay + Glicizide + Janumet	Acarbose +Glicizide + Metformin+ sitagliptin	351.33	215.33	136	0.003*
Reclimet+ istamet	Metformin +GLicizide+ sitaglipin	175	127	49.00	0.000***
Janumet (siatgliptin + metformin) + Glcinorm	Siatgliptin+ metformin+ Glicizide	240	100	130.33	0.000***

Table No 19: Average cost effective ratio of oral antidiabetic drugs.

Drug(brand)	Generic name	Cost per month	Total cost	Mean FBS reduction (mg/dl)	ACER
Monotherapy					
Glycomet	Metformin	90	3693.38	42.03	87.85
Glycinorm	Glicizide	160.73	4167.63	22.26	187.16
Gluconorm	Repaglanide	168	2658.83	7.33	3625.76
Amaryl	Glimepride	365	3619.00	19.00	190.47
Biguanides +	**Sulphonyl ureas**				
Gemer	Glimepride + metformin	328	3289.89	36.00	91.38
Glycomet + Gemer	Glimepride + metformin	372	3664	56.50	64.86
Glycomet +Dianorm	Glycomet + Glicizide	300	2010.50	18.30	109.86
Glyciphage + semiglynase	Metformin+ Glipizide	208	2966.00	19.60	151.32
Glimisave + Glycomet	Glimepride + Metformin	210	1552.50	44.83	34.62
Glycomet + Reclimet	Metformin + glicizide	285	2238.33	36.66	61.04
Glipizide + metformin	Glipizide + metformin	1225	3085.55	17.55	175.81
Glycomet +glimepride	Metformin + glimepride	406	3135.63	47.90	65.44
Glycomet + glycinorm	Metformin +glicizide	270	2687.00	80.37	33.43

Drug(brand)	Generic name	Cost per month	Total cost	Mean FBS reduction (mg/dl)	ACER
DPP4 combinations					
Glycinorm + Galvus	Glicizide + vidagliptin	780	3549	25.66	138.28
Glimepride + sitagliptin	Glimepride +sitagliptin	408	2457.00	12.60	195.00
Glycinorm +galvusmet	Glicizide + Vidagliptin + Metformin	825	4642.50	67.50	68.77
Janumet	Metformin +sitagliptin	758	4243.00	32.00	132.59
Galvusmet	Vidagliptin + Metformin	372	3664.75	56.50	64.86
Galvus + Glycomet	Vidagliptin+ Metformin	1397	3265.33	39.66	82.32
Acarbose combinations					
Glycomet + Glucobay	Metformin+Acarbose	279	2910.71	78.00	37.31
Gemer + Glucobay	Glimepride+ metformin +acarbose	936	3411.50	75.50	45.18
Glicizid + volix	Glicizide+ Voligbose	800	3903.33	65.16	59.89
Glycinorm + Glucobay	Glicizide+ Acarbsoe	342	2626.66	89.50	29.34

Drug(brand)	Generic name	Cost per month	Total cost	Mean FBS reduction (mg/dl)	ACER
More than two combinations					
Gemer+ Gluconorm	Glimepride+metformin+ Repaglinide	356	2141.50	39.87	53.70
Glucobay + Glicizide + Janumet	Acarbose +Glicizide + Metformin+ sitagliptin	737	3627.00	136	26.66
Reclimet+ istamet	Metformin +GLicizide+ Sitaglipin	892	3639.00	49.00	74.26
Janumet + Glycinorm	Siatgliptin+ metformin+ Glicizide	1490	4679.50	130.33	35.90

Table No 20: Incremental cost effective ratio of oral antidiabetics

Brand name	Generic name	Cost in one month	Mean FBS reduction (Mg/dl)	Incremental cost	Incremental effect	ICER
Monotherapy						
Glycomet	Metformin	90	42.03	3693.38s	42.03	369.038
Glycinorm	Glicizide	160.73	22.26	4167.63	19.77	210.78
Gluconorm	Repaglanide	168	7.33	26588.83	34.70	766.13
Amaryl	Glimepride	365	19.00	3619.00	23.03	157.08
Biguanides +	**Sulphonyl ureas**					
Gemer	Glimepride + metformin	328	36.00	3289.99	6.03	544.83
Glycomet + Gemer	Glimepride + metformin	372	56.50	3664.75	-14.46	-253.41
Glycomet +Dianorm	Glycomet + Glicizide	300	18.30	2010.50	23.75	84.65
Glyciphage + semiglynase	Metformin+ Glipizide	208	19.60	2996.00	22.43	132.18
Glimisave + Glycomet	Glimepride + Metformin	210	44.83	1552.50	-2.79	-555.49
Glycomet + Reclimet	Metformin + glicizide	285	36.66	2238.33	5.37	416.67
Glipizide + metformin	Glipizide + metformin	1225	17.55	3085.55	24.48	126.00
Glycomet +glimepride	Metformin + glimepride	406	47.90	3135.63	-5.87	-534.13

Glycomet + glycinorm	Metformin +glicizide	270	80.37	2687.00	-38.33	-70.08
DPP4 combination						
Glycinorm + Galvus	Glicizide + vidagliptin	780	25.66	3549.33	16.37	216.79
Glimepride + sitagliptin	Glimepride +sitagliptin	408	12.60	2457.00	29.43	83.46
Glycinorm +galvusmet	Glicizide + Vidagliptin + Metformin	825	67.50	4642.50	-25.46	-182.33
Janumet	Metformin +sitagliptin	758	32.00	4243.00	10.03	422.67
Galvusmet	Vidagliptin + Metformin	215	15.00	2557.00	27.03	94.56
Galvus + Glycomet	Vidagliptin+ Metformin	1397	39.66	3265.33	2.37	1376.32
Acarbose combination						
Glycomet + Glucobay	Metformin+Acarbose	279	78.00	2910.71	-35.96	-80.93
Gemer + Glucobay	Glimepride+ metformin +acarbose	936	75.50	3411.50	-33.46	-101.95
Glicizid + volix	Glicizide+ Voligbose	800	65.16	3903.333	-23.12	-168.77
Glycinorm + Glucobay	Glicizide+ Acarbose	342	89.50	2626.66	-47.46	-55.34
More than two combination						

Gemer+ Gluconorm	Glimepride+metformin+Repaglinide	356	39.87	2141.50	2.16	989.83
Glucobay + Glicizide + Janumet	Acarbose +Glicizide+ Metformin+ sitagliptin	737	136.00	3627.00	-93.96	-38.60
Reclimet+ istamet	Metformin + GLicizide+ sitaglipin	1446	48.80	4087.40	-6.96	-522.73
Janumet + Glycinorm	Siatgliptin+ metformin + Glicizide	1490	130.33	4679.50	-88.29	-52.99

Table No 21: Cost effectiveness analysis of oral antidiabetic drugs.

Brand	Generic	ACER	ICER	ACER/ ICER	Quadrant	Types	Result
Monotherapy							
Glycomet	Metformin	87.85	369.03	0.238	I	LC HE	Dominant
Glycinorm	Glicizide	187.16	210.78	0.887	I	LC HE	Dominant
Gluconorm	Repaglanide	3625.76	766.13	4.7315	I	LC HE	Dominant
Amaryl	Glimepride	190.47	157.08	1.212	I	LC HE	Dominant
Biguanides +	**Sulphonyl ureas**						
Gemer	Glimepride + metformin	91.38	544.83	0.1677	I	LC HE	Dominant
Glycomet + Gemer	Glimepride + metformin	64.86	-253.41	-0.2559	II	HC HE	Cost effective
Glycomet +Dianorm	Metformin+ Glicizide	109.86	84.65	1.297	I	LC HE	Dominant
Glyciphage + semiglynase	Metformin+ Glipizide	151.32	132.18	1.144	I	LC HE	Dominant
Glimisave +	Glimepride + Metformin	34.62	-555.49	-0.062	II	HC	Cost effective

Glycomet						HE	
Glycomet + Reclimet	Metformin + glicizide	61.04	416.67	0.146	I	LC HE	Dominant
Glipizide + metformin	Glipizide + metformin	175.81	126.00	1.395	I	LC HE	Dominant
Glycomet +glimepride	Metformin + glimepride	65.44	-534.13	-0.122	II	HC HE	Cost effective
Glycomet + glycinorm	Metformin +glicizide	33.43	-70.08	-0.477	II	HC HE	Cost effective
DPP4 combination							
Glycinorm + Galvus	Glicizide + vidagliptin	138.28	216.79	0.636	I	LC HE	Dominant
Glimepride + sitagliptin	Glimepride +sitagliptin	195.00	83.46	2.336	I	LC HE	Dominant
Glycinorm +galvusmet	Glicizide + Vidagliptin + Metformin	68.77	-182.33	-0.377	II	HC HE	Cost effective
Janumet	Metformin +sitagliptin	132.59	422.67	0.3136	I	LC HE	Dominant
Galvusmet	Vidagliptin + Metformin	64.86	94.56	0.685	I	LC HE	Dominant
Galvus + Glycomet	Vidagliptin+ Metformin	82.32	1376.32	0.059	I	LC HE	Dominant

Acarbose combination							
Glycomet + Glucobay	Metformin+Acarbose	37.31	-80.93	-0.4610	II	HC HE	Cost effective
Gemer + Glucobay	Glimepride+ metformin +acarbose	45.18	-101.95	-0.443	II	HC HE	Cost effective
Glicizid + volix	Glicizide+ Voligbose	59.89	-168.77	-0.354	II	HC HE	Cost effective
Glycinorm + Glucobay	Glicizide+ Acarbose	29.34	-55.34	-0.5302	II	HC HE	Cost effective
More than two combination							
Gemer+ Gluconorm	Glimepride+metformin +Repaglinide	53.70	989.83	0.054	I	LC HE	Dominant
Glucobay + Glicizide + Janumet	Acarbose +Glicizide+ Metformin+ sitagliptin	26.66	-38.60	-0.6906	II	HC HE	Dominant
Reclimet+ istamet	Metformin + GLicizide+ sitaglipin	74.26	-522.73	-0.142	II	HC HE	Cost effective
1Janumet + Glycinom	Siatgliptin+ metformin + Glicizide	35.90	-52.99	-0.677	II	HC HE	Cost effective

Table No 22: Cost of Direct medical costs incurred by Type II Diabetes Mellitus patients on oral anitidiabetics

No	Total oral antidiabetic charges incurred	Total laboratory charges incurred	Total physician charges incurred	Total complication charges incurred
210 patients	96457	207453	145850	136345
Average for one patient for one month	459.31	987.87	694.52	649.26
Total costs incurred by 210 patients	586105			

Figure No 17: Cost of Direct medical costs incurred by Type II Diabetes Mellitus patients on oral anitidiabetics

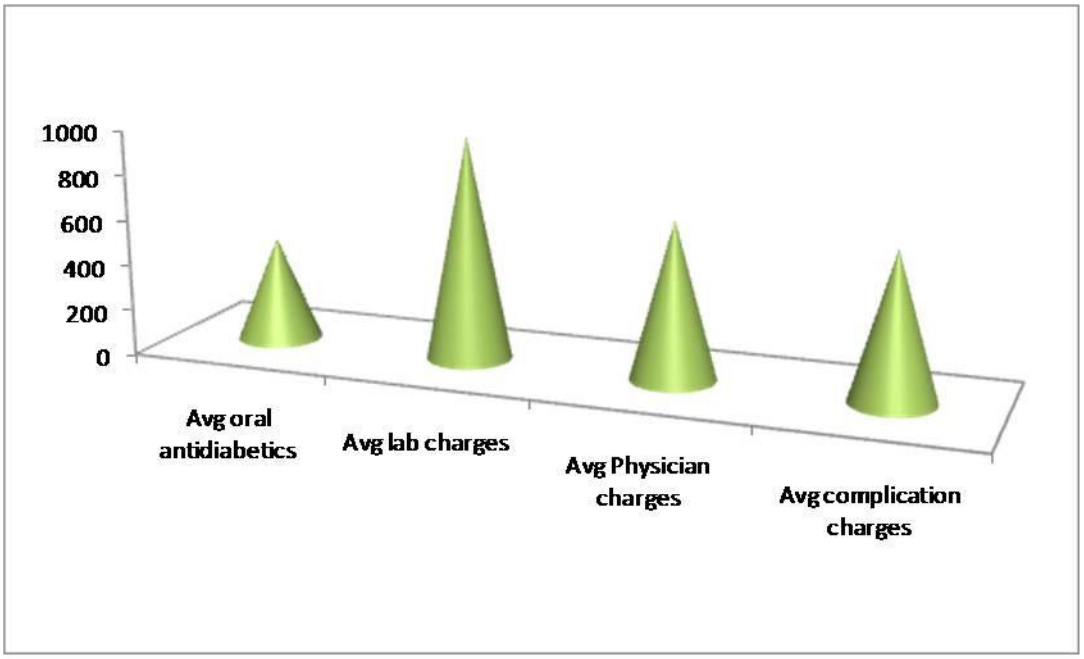
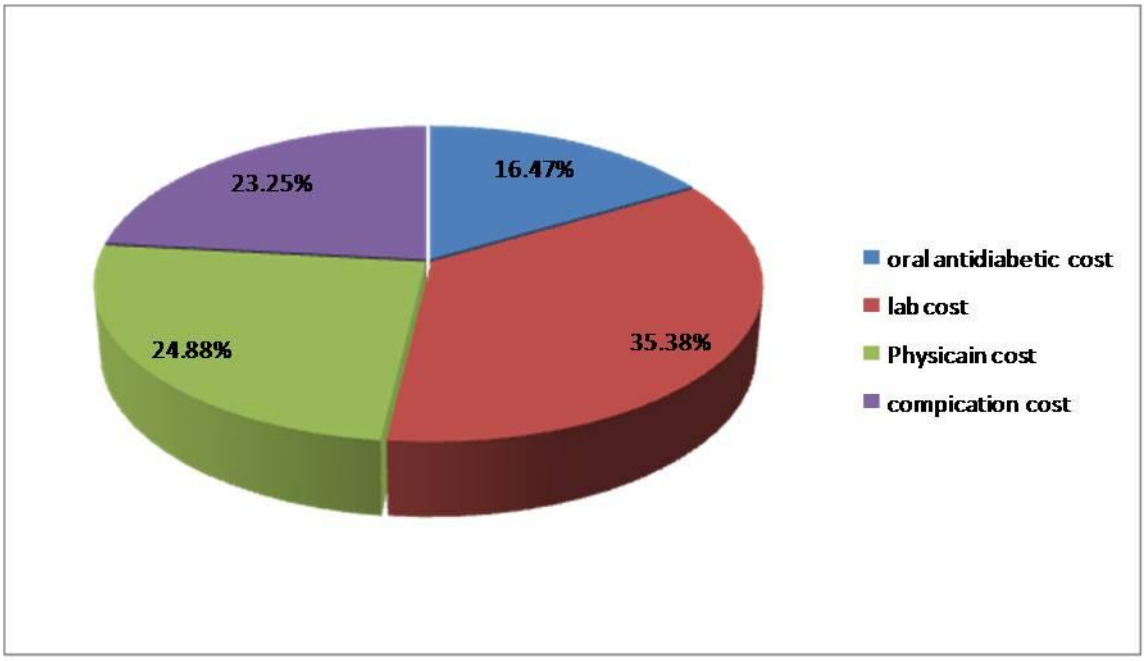


Table No 23: Average cost incurred for direct medical cost of treating DM patients on oral antidiabetics for one month

Parameter	Cost in rupees	Percentage
Oral antidiabetic drug cost	459.931	16.47%
Lab charges	987.87	35.38%
Physician charges	694.52	24.88%
Complication charges	649.26	23.25%
Average total direct cost per patient	2791.581	100%

Figure No 18: Average cost incurred for direct medical cost of treating DM patients on oral antidiabetics for one month



DISCUSSION

Research proposal approval was obtained from the Human Ethics committee of PSG Hospital. According to the study protocol, the number of patients to be studied was 303. However out of the data collected only 210 patients were fit for the inclusion criteria which included Type 2 Diabetic Mellitus patients who were on oral antidiabetics and had come for review atleast once during their therapy. It excluded patients who were lactating and pregnant or critically ill.

From the 210 patients evaluated the male were more in the study with 60% than the female (40%). This differed from most studies. It could be due to the variation of the population. Majority of patients were between the age of 60-70 years. Tri Murti et al had the same findings in a study done in Indonesia.[40] Older adults are at high risk for the development of Type 2 diabetes due to the combined effects of increasing insulin resistance and impaired pancreatic islet function with aging. Age-related insulin resistance appears to be primarily associated with adiposity, sarcopenia, and physical inactivity, which may partially explain the disproportionate success of the intensive lifestyle interventions.[49]

Diabetes Mellitus is a progressive disease with many complications. This study highlighted on the common complications the diabetic patients have. Hypertension was the most common complication with 47% followed by diabetic foot ulcer15% and dyslipidemia 11.3%, ACS (9.5%), UTI (5.2%) and COPD(7.4%). Abdelaziz et al also had majority of the study patients having hypertension.[11] Though it should be noted that hypertension may not always be a complication of DM. Some patients might have had HTN before DM diagnosis. However research heavily suggests that too much sugar may lead to hypertension. The excess sugars lead to weight gain which becomes a potential for high blood pressure. The high blood pressure propagates many complications e.g. ACS, hypertensive retinopathy, neuropathy. Therefore diab etic patients should make sure their blood pressure levels are within the charts.

A study done by Sudha et al showed that biguanides were the most prescribed antidiabetic drugs.[41] This was the case with this study which showed that biguanides were the mostly prescribed drugs both as a monotherapy and combination therapy. 28.2% patients received metformin monotherapy and most of the combination drugs had metfromin. This is due

to the effectiveness of metformin in blood sugar reduction and its benefit in reducing the CVD risk as well as the safety of the therapy. The least prescribed monotherapy was thiazolidinediones (TZD) (2.38%). This could be due to the one too many side effects it has. Common side effects associated with TZDs include edema, weight gain, macular edema and heart failure. Moreover, they may cause hypoglycemia when combined with other antidiabetic drugs as well as decrease hematocrit and hemoglobin levels. Increased bone fracture risk is another TZD-related side effect.

Combination of sulphonyl ureas and biguanides were the most used combinations in this study. Table No 10 and figure No 7 show 28% prevalence of the same. Akshay et al concluded in their study that biguanide and sulphonyl ureas were the most prescribed combinations. This could be because of the different mechanism of action and the synergistic effect both drugs have on each other. Biguanides lowers blood sugar by decreasing the making muscle tissue more sensitive to insulin so that glucose can be absorbed. Sulphonyl ureas stimulate the beta cells of the pancreas to secrete more insulin.[40]

The least common combination was that of biguanides and the DPP4 inhibitors. (1.45%) DPP4 inhibitors are initiated as a 3rd line agent in patients with higher post prandial glucose as they effectively reduce it. The most commonly prescribed anti diabetic agents along with Gliptins is Metformin, followed by Sulphonyl ureas, as a combination pill, use of Metformin and Sitagliptin is common.[42]Sitagliptin and metformin provide additive glycemic improvements, suggesting a synergy between the agents. However, although sitagliptin is effective, its cost and limited long-term data may restrict its use.[50] Other combinations seen in this study were sulphonyl ureas and DPP4 inhibitors(10.38%), and Alpha glucosidase inhibitors with biguanides and sulphonyl ureas (10.95%)

Adding a second drug is usually better than increasing the dosage of an agent that has already been given in a nearly maximum dosage. In some patients three drugs.[43] Three combination antidiabetic drug was utilized up to 10.74% of the total prescriptions. This is because three drugs therapy give a better control of blood sugar. A study has shown that three drug therapy is not common practice. However, three oral agents (e.g. metformin, sulfonylurea, pioglitazone) can be considered in patients with A1C values that are not too far from goal (A1C $\leq$8.5 percent).[52]

The cost of the antidiabetic therapy was calculated over a period of one month. These charges of the different therapies were reached upon by getting the average of the costs of the different prescribed brands. In the monotherapy the average cost of metformin was found to be the cheapest at Rs 90 per month and Glimepride was the most expensive monotherapy at an average cost of Rs 189 as seen in Table 13and Figure 12. Study conducted at John Hopkins University Research concluded that Metformin is the safest and cheapest oral antidiabetic drug.[44] Repaglanide had average cost of Rs 168 per month and Glicizide had an average cost of Rs 160 per month.

In the combination of sulphonyl ureas and biguanides, Glimepride and Metformin combinations were more expensive (Rs 335) than that of Glicizide and Metformin (Rs 254.4) in Table No 14 and Figure 13. DPP4 combinations with metformin were less expensive at Rs 397.4 than that of DPP4 and sulphonyl ureas (Rs 671) This could be due to the fact that biguanides are much cheaper than sulphonyl ureas. The acarbose combinations were cheaper with metformin (Rs 279) than with sulphonyl ureas (Rs 342) as seen in Table 16 and Figure 15.

This study considered the effectiveness of the oral antidiabetics by taking FBS as the unit of observation in the diabetic patients. This is because all patients had their FBS values evaluated and reviewed after a month unlike the other units of reduction. Table 17 and Figure 16 shows the laboratory investigations the patients underwent. Majority of patients had both the FBS and PPBS evaluated. Singh et al conducted a study on pharmacoeconomic and drug utilization of antidiabetic drugs and used Fasting Blood Sugar to evaluate the effectiveness of the antidiabetics. [28]The ADA has recognized the fasting plasma glucose (FPG), as the diagnostic test of choice. PPBS values can change due to many variables, such as physical activity, insulin sensitivity, gastric emptying rate, and meal composition .HbA1c is not recommended as a diagnostic or a screening test because it is considered that HbA1c is inferior to FPG or post-load glucose values at predicting type 2 diabetes because the existence of hemoglobin or red cell abnormalities can increase the variability of HbA1c values.[51]

Table No 18 show the calculated effectiveness of the given oral antidiabetic drugs using the p value. In the monotherapy, Metformin was the most effective drug with a p value of 0.001 and an average FBS reduction of 42 mg/dl as compared to the sulphonyl ureas and

thiazolidinediones which had a p value of 0.228 and 0.303 respectively and an average FBS reduction of 19 and 7 mg/dl respectively from the baseline value.

In combination drugs the Biguanides and sulphonyl ureas show significant effectiveness with the combinations of Glimepride and metformin in different brand names with a p value of 0.000.The acarbose and metformin combinations have more effectivenesss (p value=0.000)than acarbose and sulphonyl ureas(p value =0.001). The two combination drugs have more effectiveness than monotherapy. And the more than two drugs have the most effectiveness when compared to the single and two combination therapy. Most three drugs combinations have a p value of 0.000.This is a proven fact on a study done by Rajeshwari et al.[43] The three drug therapy containing Metformin, Glicizide and Sitagliptin had the most effectiveness . Also the combination of Metformin, Glimepride and Repaglanide.

To determine the cost effective therapy the ACER and ICER were calculated as shown in Table 19 and 20. In an ICER quadrant one of the four responses are available: Quadrant 1 is dominant which has low cost and high effect drugs. Quadrant II is Cost Effective with High cost and high Effect. Quadrant III is the Excluded category has drugs with high cost and low effect. Quadrant IV has Questionable drugs which have the low cost and low effect. Monotherapies were all found in the Quadrant I which suggests they are all of low cost and high effect. The cost effective therapies in Quadrant II had high cost and high effect and were found to be Glimepride and metformin and the acarbose combinations ie. Acarbose and Metformin and Acarbose and Glicizide as well as the three drug combinations. A study done by Abdelaziz et al also reported that Glimepride and metformin were the most cost effective combination therapy.[11] Study done in Chinese patients supported the use of Acarbose in combination with Metformin and found out that Acarbose is as safe and effective as Metformin, Vidagliptin and Glimepride and also has benefits on reducing the CVD risk.[48]

This study also undertook to calculate the cost of illness incurred by the ambulatory diabetic patients who were taking oral antidiabetics. The total medical cost incurred for the 210 patients over a period of one month was 5.86 lakhs and was arrived at by calculating the total costs of drugs, laboratory charges, physician charges and complications charges. The average total medical cost incurred by a single ambulatory patient was Rs 2791.58. The laboratory charges took the largest part of the cost incurred by patients (35.38%) This could be explained by

the fact that majority of diabetic patients have complications and these complications are reviewed by several laboratory values. The physician charges were the second highest charges incurred at 24.88%. This may be explained by frequent visits patients make due to complication of disease. The complication charges come in third with 23.25% of total cost. DM direct treatment cost increases with presence and progression of DM related complications. [16] The oral antidiabetics were the least incurred costs with 16.47% of total costs.

This finding varies from other studies which had the average cost incurred by one patient to be Rs 7386. [11] This variation could be due to the fact that the study considered the costs of hospitalization and nurses where as this study only included the direct medical cost incurred by ambulatory patients thus the hospitalization and nurses charges were not included.

Indirect costs were not included in this study but it is important to note that these are also costs that the diabetic patients incur. The indirect costs typically consist of work loss, worker replacement, and reduced productivity from illness and disease. Due to disease patients end up having lost work days which account for the indirect costs.

CONCLUSION

Diabetes Mellitus is a chronic and progressive disorder which affects patients for a life time and this is why it should be a burden to the medical faculty to come up with effective yet affordable means of treating this growing pandemic. Effective means because diabetes is a progressive disease with a series of complications that come if the blood sugar is poorly controlled. Affordable means to treat the disease because this is a disease a patient has to deal with for a lifetime once diagnosed. Hence this becomes a need and not a want that the patients have to fulfill. Making drugs affordable for patients to be able to easily access regardless of economic status should be a priority for the medical team.

The study concluded that the male patients were more than the female patients and that most of the Type II Diabetes Mellitus were between the age of 60-70 years. Hypertension was the major complication the diabetic patients had in this study followed closely by diabetic foot ulcer.

This study has sought to come up with the most effective yet affordable oral antidiabetic drugs. The combination therapy was more prescribed than the monotherapy in this study. The study has concluded that the combination of Glimepride and metformin is a cost effective therapy.

The acarbose combinations were also cost effective according to this study. However the acarbose combinations are rarely used. Studies have supported the effective use of acarbose in clinical practice because of their safety and benefits such as reducing the risk of CVD and do not cause weight gain. Therefore acarbose and its combinations should be considered for therapy which is not a common practice as of now.

Three drug combinations also have been seen to be cost effective in this study. Instead of going to insulin therapy the three oral drug therapy should be utilized unless the blood sugar is not controlled by oral antidiabetics. However if patient is controlling blood sugar efficiently with 3 oral hypoglycemic agents this should be maintained and constant monitoring to be done.

This study found out that the cost of illness incurred in one month by an individual patient was averagely Rs 2781.58. This is a huge amount considering it only involves

the medical costs ambulatory patients paid. Hence treating diabetes is quite expensive. However to efficiently establish the economic burden to the patients, the patients income has to be known. Thus efforts to reduce this burden of the disease should be employed. This should include actively talking about the disease and encouraging healthy eating habits and living. Physicians should employ cost effective therapy options and the pharmacists should take on their role seriously in patient education in both rural and urban areas. Patients should be taught on importance of being compliant to drugs to keep the blood sugar level controlled. Finally the government of India should help in health insurance to help share the economic burden with the patients.

Clinical pharmacists have a role to play in the effort to lower the economic burden of the disease. By making this disease aware to the society to avoid more people being affected and also educating the patients on the disease knowledge and the importance of patient compliance to help prevent the progression of the disease. Clinical pharmacists also have a role to play in advising the physicians on the cost effective therapies available.

LIMITATIONS OF THE STUDY

- The study did not include indirect costs incurred by the diabetic patients whereas this is a cost that diabetic patients have to incur due to loss of work days, loss of productivity because of the disease manifestations.
- For cost effective analysis more number of patients have to be used to calculate effective cost effectiveness.
- A prospective study would have provided more data especially on the indirect costs incurred by the patients.
- Lack of adequately being able to know the patients income to come up with efficient economic burden on a particular patient.

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To
Ms Mkoji Prudence Shambi
II M Pharm
Guide: Mrs P Rama
PSG College of Pharmacy
Coimbatore 641 004

Ref: Project No.16/340

Date: October 18, 2016

Dear Ms Mkoji Prudence Shambi,

Institutional Human Ethics Committee, PSG IMS&R reviewed and discussed your application dated 06.10.2016 to conduct the research study entitled "*Pharmacoeconomic evaluation of oral antidiabetics in ambulatory patients in tertiary care hospital*" during the IHEC meeting held on 07.10.2016.

The following documents were reviewed and approved:

1. Project submission form
2. Study protocol (Version 1.1 dated 17.10.2016)
3. Confidentiality statement
4. Application for waiver of consent
5. Data collection tool (Version 1.1 dated 17.10.2016)
6. Permission letter from the Dean
7. Current CVs of Principal investigator, Co-investigator
8. Budget

The following members of the Institutional Human Ethics Committee (IHEC) were present at the meeting held on 07.10.2016 at IHEC Secretariat, PSG IMS & R between 10.00 am and 11.00 am:

Sl. No.	Name of the Member of IHEC	Qualification	Area of Expertise	Gender	Affiliation to the Institution Yes/No	Present at the meeting Yes/No
1	Mr R Nandakumar (Chairperson, IHEC)	BA., BL	Legal Expert	Male	No	Yes
2	Dr. S. Bhuvaneshwari (Member-Secretary, IHEC)	MD	Clinical Pharmacology	Female	Yes	Yes
3	Dr S Shanthakumari	MD	Pathology, Ethicist	Female	Yes	Yes
4	Dr Sudha Ramalingam	MD	Epidemiologist, Ethicist Alt. member-Secretary	Female	Yes	Yes
5	Dr D Vijaya	M Sc., Ph D	Basic Medical Sciences (Biochemistry)	Female	Yes	Yes

The study is approved in its presented form. The decision was arrived at through consensus. Neither PI nor any of proposed study team members were present during the decision making of the IHEC. The IHEC functions in accordance with the ICH-GCP/ICMR/Schedule Y guidelines. The approval is valid until one year from the date of sanction. You may make a written request for renewal / extension of the validity, along with the submission of status report as decided by the IHEC.

PSG Institute of Medical Sciences & Research
Institutional Human Ethics Committee

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Following points must be noted:

1. IHEC should be informed of the date of initiation of the study
2. Status report of the study should be submitted to the IHEC every 12 months
3. PI and other investigators should co-operate fully with IHEC, who will monitor the trial from time to time
4. At the time of PI's retirement/intention to leave the institute, study responsibility should be transferred to a colleague after obtaining clearance from HOD, Status report, including accounts details should be submitted to IHEC and extramural sponsors
5. In case of any new information or any SAE, which could affect any study, must be informed to IHEC and sponsors. The PI should report SAEs occurred for IHEC approved studies within 7 days of the occurrence of the SAE. If the SAE is 'Death', the IHEC Secretariat will receive the SAE reporting form within 24 hours of the occurrence
6. In the event of any protocol amendments, IHEC must be informed and the amendments should be highlighted in clear terms as follows:
   a. The exact alteration/amendment should be specified and indicated where the amendment occurred in the original project. (Page no. Clause no. etc.)
   b. Alteration in the budgetary status should be clearly indicated and the revised budget form should be submitted
   c. If the amendments require a change in the consent form, the copy of revised Consent Form should be submitted to Ethics Committee for approval
   d. If the amendment demands a re-look at the toxicity or side effects to patients, the same should be documented
   e. If there are any amendments in the trial design, these must be incorporated in the protocol, and other study documents. These revised documents should be submitted for approval of the IHEC and only then can they be implemented
   f. Any deviation-Violation/waiver in the protocol must be informed to the IHEC within the stipulated period for review
7. Final report along with summary of findings and presentations/publications if any on closure of the study should be submitted to IHEC

Kindly note this approval is subject to ratification in the forthcoming full board review meeting of the IHEC.

Thanking You,

Yours Sincerely,

SECRETARY
PSG IMS&R
COIMBATORE-641004.
INSTITUTIONAL HUMAN ETHICS COMMITTEE

Dr S Bhuvaneshwari
Member - Secretary
Institutional Human Ethics Committee

Avinashilingam
Institute for Home Science and Higher Education for Women
University
(Estd. u/s 3 of UGC Act 1956)
Coimbatore - 641 043, Tamil Nadu, India
(Deemed University under Category 'A' by MHRD)
Re-accredited with 'A' Grade by NAAC

Certificate of Participation

This is to certify that Mr./Ms. Mkoji Prudence Phambi

has participated in the Indian Council of Medical Research (ICMR) sponsored one day National symposium on ***"Current Trends in Gynec Oncology"*** *organized by the Department of Physician Assistant on* ***23rd February 2017.***

Organising Secretary

Co-ordinator

Registrar

PSG COLLEGE OF PHARMACY

COIMBATORE 641 004

UNIVERSITY ACCREDITED CONTINUING PHARMACY EDUCATION (CPE) PROGRAM

This is to certify that PRUDENCE SHAMBI

has participated in the educational activity titled RESEARCH METHODOLOGY *on* 24-01-17

held at PSG College of Pharmacy, Seminar Hall, Coimbatore

This activity has been reviewed and accepted by the ***Centre for Accreditation,*** *The Tamil Nadu Dr. M.G.R. Medical University, Chennai designates this educational activity for a maximum of CPE Credit points* 10 *in Category* II

Principal

Organizing Secretary